

PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

(Attorney Docket No. SIR-MIS-00001-US-CIP[3])

IN THE APPLICATION OF:)		
)		
McSwiggen <i>et al.</i>)		
)		
Serial No.: 10/720,448)	Examiner:	BOWMAN, Amy
)		Hudson
Filed: November 24, 2003)	Group Art Unit:	1635
)		
)		
Title RNA Interference Mediated)	Confirmation No.:	4875
Inhibition of Gene Expression)		
Using Chemically Modified)		
Short Interfering Nucleic Acid)		
(siNA))		

REPLY BRIEF UNDER 37 C.F.R. §41.41

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Reply Brief is filed in response to the Examiner's Answer mailed on October 20, 2010. No fee is thought to be presently due, but the Commissioner is authorized to charge payment of any additional fees required in connection with the paper(s) transmitted herewith, or to credit any overpayment of the same, to Deposit Account No. 50-4615.

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REAL PARTY IN INTEREST

The real party in interest is Sirna Therapeutics Inc., a wholly owned subsidiary of Merck & Co., Inc.

RELATED APPEALS AND INTERFERENCES

Appeal No. 2009-2562, resulting from application No. 90/008,177 (Re-examination of US Patent 7,022,828). A copy of the Board's decision is attached as Appendix C.

STATUS OF CLAIMS

A Final Office Action was mailed on July 12, 2010. Claims 52 and 54-64 stand rejected and are presently pending. Claims 1-51 and 53 were previously canceled. The rejections of claims 52 and 54-64 are appealed with this submission. A copy of the claims on appeal is attached in Appendix A.

STATUS OF AMENDMENTS

No claims are amended.

SUMMARY OF THE CLAIMED SUBJECT MATTER

The invention provides certain chemically modified short interfering RNA (siRNA) molecules having a sense strand and an antisense strand that mediate RNA interference. Each strand of the claimed siRNA molecules is between 18 and 24 nucleotides in length. Each strand comprises 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides. Additionally, the sense strand includes a terminal cap moiety at the 3'-end, the 5'-end, or both 5' and 3' ends of the sense strand. Furthermore, 10 or more pyrimidine nucleotides of the sense strand and/or antisense strand are chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides. See claims 52 and 59; Specification at, inter alia, page 28, lines 12-29; and page 81, lines 8-10. See additionally Figures 18 and 19; Table I (beginning at page 223) and Table IV (page 235) for numerous examples of the presently claimed chemically modified nucleic acid molecules.

Each strand of the chemically modified siRNA molecules described above can be further modified with 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphorothioate internucleotide linkages. *See* claims 54, 55, 60, and 61; Specification at, *inter alia*, page 28, lines 12-29; Figures 18 and 19; Table I (beginning at page 223) and Table IV (page 235).

Ten or more of the pyrimidine nucleotides in the sense and/or antisense strand of each of the modified double stranded nucleic acid molecules can be a 2'-O-methyl pyrimidine nucleotide. *See* claims 57 and 63; Specification at, *inter alia*, page 28, lines 24-26; Figures 18 and 19 (A, B, C); Table I (beginning at page 223) and Table IV (page 235) *e.g.*, "Stab 6" and "Stab 17".

Ten or more of the pyrimidine nucleotides in the sense and/or antisense strand of each of the modified double stranded nucleic acid molecules can be a 2'-deoxy-2'-fluoro pyrimidine nucleotide. *See* claims 58 and 64; Specification at, *inter alia*, page 28, lines 24-26; Figures 18 and 19 (A, B, C, D, E, F); Table I (beginning at page 223) and Table IV (page 235) *e.g.*, "Stab 3", "Stab 4", "Stab 5", "Stab 7", "Stab 8", "Stab 11", "Stab 12", "Stab 13", "Stab 14", and "Stab 18".

The present invention also pertains to a composition comprising one of the molecules depicted above in a pharmaceutically acceptable carrier or diluent. *See* claims 56 and 62; Specification at, *inter alia*, page 18, lines 26-27.

GROUND OF REJECTION TO BE REVIEWED ON APPEAL

The issues on appeal are:

- (I) Whether claims 52 and 54-64 are obvious under 35 U.S.C. § 103(a) over Elbashir (EMBO J., 2001, 20(23):6877) in view of Nyce (WO 99/13886), Parrish (Molecular Cell, 2000, 6:1077-87), Matulic-Adamic (US 5,998,203), Bertrand (Biochemical & Biophysical Research Commun., 2002, 296:1000-1004); Braasch (Biochemistry, 2002, 41(14):4503-4510), and Olie (Biochimica et Biophysica Acta, 2002, 1576:101-109).
- (II) Whether claims 52 and 54-64 require a terminal disclaimer in view of the provisional obviousness-type double patenting rejection over Applicant's USSN 12/170,290; 12/185,652; 12/204,572; 12/203,055; 12/200,736; 12/203,731; 12/204,612; 12/175,367; and 10/444,853 applications.

ARGUMENT

I. Claims 52 and 54-64 are inventive and not obvious

In response to the Examiner's Answer mailed October 20, 2010, and as set forth in the Appeal Brief filed August 11, 2010, Applicant maintains that the present invention is clearly inventive and non-obvious. The pioneering discovery of RNA interference (RNAi) by Fire and Mello (see US Patent No. 6,506,559) provided a revolutionary new approach to inhibit the expression of any given gene. This discovery was recognized by the 2006 Nobel Prize in physiology or medicine. Nevertheless, as is often the case with pioneering discoveries in medicine, additional sequential innovation was required to advance the technology from the laboratory to the clinic. Indeed, the later discovery of short interfering RNA (siRNA) by Tuschl, Zamore, Sharp, and Bartel (see US Application No. 20020086356, "Tuschl I") identified the molecular triggers of the RNAi mechanism. Subsequent work by Tuschl, Elbashir, and Lendeckel (see US Application No. 20040229266, "Tuschl II") sought to further characterize and optimize the RNAi triggers. The results of this characterization and optimization were summarized in a "The siRNA User Guide," (see US Application No. 20040229266, page 49; see also Elbashir et al., EMBO J., 2001, 20(23):6885) which provided the state of the art siRNA molecules at the time of the instant invention.

These state of the art siRNA molecules were stabilized with 2'-deoxy modification of the 3'-terminal overhang regions of the duplex. Specifically, "2'-deoxy substitutions of the 2 nt 3'-overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNase resistance of siRNA duplexes" (see Elbashir, EMBO J., 2001, 20(23): 6885). Attempts at more extensive modification, i.e., beyond the 3'-termini, was taught to "*reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly*" (Id). When tested by Applicant, the state of the art siRNA taught by Elbashir having modified 3'-terminal overhangs demonstrated a half life in human serum of only 15 seconds. While such molecules may be useful as a research tool *in vitro*, they would not have utility as part of a therapeutic regimen. On the other hand, extensively modified siRNA

molecules of the instant invention, having ~50-100% modification of each strand with a focus on pyrimidine modifications combined with terminal cap modification of the sense strand, have demonstrated serum half lives of up to 40 days (*see* Figure 3 of the instant application; *see* also Figure 3 of the earliest priority document recognized by the Office, USSN 60/408,378 filed September 5, 2002; *see* also Figure 3 of USSN 60/358,580 filed February 20, 2002 to which Applicant has previously asserted priority and which shows an increase in serum half life from 15 seconds to 72 hours). Furthermore, these extensively modified siRNA molecules show surprisingly robust RNAi activity that is equivalent or even improved compared to the state of the art at the time of filing (*see* **Figures 3, 14, 15, 28, 29, and 30** and discussion thereof *infra* at page 21).

The present invention has significantly advanced the state of the art by providing synthetic siRNA molecules that are extensively modified yet which surprisingly maintain robust or improved RNA interference activity, thus enabling the use of such molecules as therapeutic modalities. The Office maintains that this significant advancement over the prior art resulted merely from "routine optimization," and alleges that the invention is *prima facie* obvious. Specifically, claims 52 and 54-64 continue to stand rejected under 35 U.S.C. 103(a) as allegedly being obvious in view of Elbashir (EMBO J., 2001, 20(23):6877), Nyce (WO 99/13886), Parrish (Molecular Cell, 2000, 6:1077-87), Matulic-Adamic (US 5,998,203), Bertrand (Biochemical & Biophysical Research Commun., 2002, 296:1000-1004); Braasch (Biochemistry, 2002, 41(14):4503-4510), and Olie (Biochimica et Biophysica Acta, 2002, 1576:101-109). *See* Examiner's Answer, page 4. Applicant respectfully traverses and relies upon well established jurisprudence, as discussed below, to prove otherwise.

Applicant maintains that the presently claimed invention cannot be obvious for at least three reasons as set forth in the Appeal Brief filed August 11, 2010. First, one of skill in the art would *not have had any reasonable expectation of success* in practicing the claimed invention because the prior art either taught away from the claimed invention or indicated a high level of unpredictability that would have precluded any reasonable expectation of success. Second, it is impermissible hindsight to conclude that the present invention is obvious because it would have been "obvious to try" using combinations of

known modifications via "routine optimization," especially since the prior art gave "*no direction as to which of many possible choices is likely to be successful*" and offered "*only general guidance as to the particular form of the claimed invention or how to achieve it.*" *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Finally, even if a *prima facie* finding of obviousness could be established, the *failure of others*, along with the *surprising results* obtained in practicing the invention, serve to effectively rebut any such presumption of obviousness.

1. No reasonable expectation of success

The Office alleges (*see* Examiner's Answer, page 24):

"There would have certainly been a reasonable expectation of activity within the instantly claimed genus of molecules given the motivation to routinely optimize siRNA molecules via balancing stability and activity wherein the molecules are readily tested and screened via routine techniques in the art. One would reasonably expect that routine optimization via adding modifications to test for stability and preservation of half life would result in active molecules when utilizing modifications that are routinely utilized to enhance the activity of nucleic acid inhibitory molecules.

Applicant respectfully traverses and maintains that one of skill in the art at the time of the invention would not have any reasonable expectation of success in practicing the claimed invention because of the teaching away and high level of unpredictability provided by the cited art with respect to the ability of extensively modified siRNA to mediate RNA interference. MPEP § 2143.03(VI) states that "[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." A reference will teach away when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of the applicant's invention. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Here, because the Elbashir reference discloses problems with respect to more extensive modification beyond the 3'-terminal portions of a siRNA, and because these teachings are based on the proposed RNAi mechanism as it was understood at the time of the invention, one of skill in the art would not be inclined to extensively modify siRNA molecules nor have any reasonable expectation of success in doing so. As such, the teachings of Elbashir et al., as a whole, teach away from the instantly claimed invention that requires significant modification far beyond the 3'-terminal overhang portions of a siRNA duplex.

The Office, on the other hand, maintains that "the only thing that Elbashir et al. teaches away from is 100% modification of one or both strands with 2'-deoxy only or 2'-O-methyl only" and that "[a]lthough applicant continues to read the passage on page 6885 of Elbashir et al. out of context, the only 'more extensive' modification that could be referred to is the complete modification of one or both strands, as from a fully reading of the article is the only modification that was tested outside of the 2 or 4 nucleotides on each end." Examiner's Answer, page 20. On the contrary, Applicant maintains that at the time of the invention, Elbashir et al. as a whole effectively taught away from one of skill in the art making and using active siRNA duplexes that are extensively modified when compared to the duplexes shown in Figure 4 of the reference that were capable of maintaining RNAi activity.

Elbashir *et al.* described siRNA duplexes having from 9.5% to 100% of the nucleotides modified in each strand by replacing the 2'-hydroxyl group of said nucleotides with either 2'-deoxy or 2'-O-methyl. Figure 4 shows that when the two, overhanging 3' nucleotides of each strand were modified (representing 9.5% of duplex nucleotides) with 2'-deoxy nucleotides, RNAi activity was maintained. The same result was found when the two additional nucleotides adjacent to the 3' overhangs of each strand were modified (representing 19% of the duplex nucleotides). However, when either one strand of the duplex was modified (representing 50% of the duplex nucleotides) or both strands of the duplex were modified (representing 100% of the duplex nucleotides), RNAi activity was abolished. The authors summarize their findings in the Discussion section of the paper under the heading "The siRNA user guide" providing specific guidance to those skilled in the art for generating siRNA duplexes that are more palatable from a manufacturing cost perspective, and which may have enhanced resistance to nuclease degradation. The authors state on page 6885, with emphasis added, the following:

*Efficiently silencing siRNA duplexes are composed of 21 nt sense and 21 nt antisense siRNAs and **must** be selected to form a 19 bp double helix with 2 nt 3'-overhanging ends. 2'-deoxy substitutions of the 2 nt 3'-overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNase resistance of siRNA duplexes. **More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly.***

It should be noted that the teachings of the Elbashir reference have been reviewed by the BPAI (see attached decision, Appendix C) who found that "[a] fair reading of [Elbashir]...is that more extensive 2'-deoxy or 2'-O-methyl modifications beyond the two nucleotide 3'-overhang reduces the ability of siRNAs to mediate RNAi." Appeal 2009-002562, at page 27. This fair reading is consistent with the position that extensive modification and, in particular, modification beyond the 3'-terminal regions of one or both strands of a siRNA molecule, is either expressly taught away from, or in the alternative, is highly unpredictable in view of the teachings of Elbashir et al., especially since their conclusions were premised on mechanistic incompatibility, i.e., that more extensive modifications interfere with protein association for siRNP assembly.

Citing *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314 (Fed. Cir. 2009), the Office recognized in the Examination Guidelines Update: Developments in the Obviousness Inquiry After *KSR v. Teleflex* (Notices) that, "[a]n inference that a claimed combination would not have been obvious is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements." Fed. Reg. 75:169 (September 1, 2010) page 53649. Clearly, one of skill in the art, having read the teachings of Elbashir et al., who warn against more extensive modification beyond the 3'-terminal regions due to proposed mechanistic concerns over the ability of the siRNA to associate with proteins required for RNAi, and who explicitly show that modification of ~50-100% of the nucleotide positions of the siRNA duplex abolished RNAi activity, would certainly not have any reasonable expectation of success in arriving at active molecules with ~50% or greater levels of modification of each strand (i.e., 10 or more modified nucleotides in each strand). The reasonable expectation of success is diminished further when one considers the other limitations of the independent claims, i.e. the requirement of a 3', 5', or both 3' and 5' terminal caps on the sense strand, and the requirement of having 10 or more modified pyrimidine nucleotides in the sense and antisense strand (Claim 52) or alternately 10 or more modified pyrimidine nucleotides in the sense or antisense strand (Claim 59).

The Office on the other hand alleges that the Board's interpretation of "The siRNA user guide" is consistent with the position that the Elbashir reference only teaches away from 100% modification with 2'-deoxy or 2'-O-methyl because "[s]tating that complete substitution abolished RNAi is not the same of [*sic*] stating that any 2'-O-methyl modification should be avoided." Examiner's Answer, page 21. The Office appears to confuse the issue before the Board in the related appeal (Reexamination control 90/008,177, Patent 7,022,858) with the issue currently at hand. The claims reviewed in the related appeal only required a single 2'-O-methyl modification in addition to a single 2'-deoxy-2'-fluoro modification, i.e., only two modifications in total. In comparison, the instant claims require 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modifications in each strand, a terminal cap at the 3', 5', or both 3' and 5' ends of the sense strand, and 10 or more pyrimidine nucleotides of the sense and antisense strand (Claim 52), or the sense or antisense strand (Claim 59), modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro, i.e. greater than 20 modifications in total. Thus, Applicant's arguments do not rest on a teaching away premised on "any" 2'-O-methyl modification which could be limited to two nucleotides of the terminal 3'-overhang regions, but rather a teaching away premised on more extensive modification (~50% or greater modification) that would necessarily require significant alteration well beyond any terminal 3'-overhang portions in each strand of the siRNA.

The Office incorrectly asserts that "[t]he minimum required by the instant claims in fact is not far off from what was exemplified to work by Elbashir et al., given that the instant modifications can be concentrated in the terminal regions." Examiner's Answer, page 23. However, the current claims require modification of (1) the sense strand with 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides and a terminal cap molecule at the 3'-end, the 5'-end, or both 3' and 5'-ends of the sense strand; in addition to (2) modification of the antisense strand with 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides; in addition to (3) modification of 10 or more pyrimidine nucleotides of the sense and antisense strand (Claim 52) or (4) modification of 10 or more pyrimidine nucleotides of the sense or antisense strand (Claim 59). It is difficult to imagine how the instantly claimed requirements would be concentrated only at the 3'-terminal regions as taught by

Elbashir et al. as the only exemplification of successful modification in Elbashir is limited to modification of two nucleotides of the single stranded 3'-overhang and up to two adjacent nucleotides (up to 4 nucleotides at the 3'-terminus of each strand).

There is simply no teaching or suggestion provided by Elbashir of any successful modification beyond the 2-4 nucleotides at the 3'-terminus of each strand. Any suggestion by the office that Elbashir teaches successful modification of the 5'-ends is misplaced. A proper reading of Elbashir et al. reveals that RNAi activity of duplexes with more extensive modification reaching the 5'-terminus (which would be expected to interfere with terminal 5'-end phosphorylation by enzymes that recognize the siRNA duplex) cannot be restored even with 5'-phosphorylation (see Elbashir et al., page 6886).

It was recently demonstrated that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA function and that ATP is used to maintain the 5'-phosphates of the siRNAs (Nykänen et al., 2001). However, 5'-phosphorylation of fully 2'-deoxy- or 2'-O-methyl-modified siRNA strands was not able to restore RNAi (data not shown). Unmodified siRNA duplexes with free 5'-hydroxyls and 2 nt 3' overhangs are readily phosphorylated in D.melanogaster embryo lysate (Nykänen et al., 2001). In this respect, it should be noted that our reported RNAi efficiencies were determined by pre-incubating the siRNA duplexes for 15 min in D.melanogaster lysate before adding target and control mRNAs, thus providing sufficient time for 5'-phosphorylation of siRNA duplexes to occur. Comparison of the RNAi efficiencies of 5'-phosphorylated and 5'-non-phosphorylated siRNAs (for duplexes shown in Figures 1E, F and Figure 2C) did not reveal any sizeable differences (data not shown).

Therefore, the Office's assertion that "[t]he minimum required by the instant claims in fact is not far off from what was exemplified to work by Elbashir et al., given that the instant modifications can be concentrated in the terminal regions" simply cannot stand in view of the actual teachings provided by Elbashir et al. because (1) Elbashir et al. does not teach successful 5'-terminal modification, and (2) Elbashir et al. teaches that activity of more extensively modified duplexes cannot be restored even with 5'-end phosphorylation.

Regarding Parrish, the Office notes that the authors teach 742 nt long dsRNA with complete modification with 2'-fluorouracil modifications and alleges that "it is noted that the instant claims do not recite any upper length limitation." Examiner's Answer, page 7. Applicant respectfully traverses, as independent claims 52 and 59 clearly recite the

limitation "each strand is between 18 and 24 nucleotides in length." Furthermore, the Office continues to incorrectly allege that "Parrish specifically teaches 2'-deoxy incorporation with strong RNA interference activity." Examiner's Answer, page 24. Yet, Parrish clearly shows that in all instances where 2'-deoxy modifications were incorporated, RNAi activity was abolished or substantially decreased (see Parrish et al., Figure 5B and discussion on page 1081; and similarly interpreted by Elbashir et al., as evidenced by the passage reproduced below).

More importantly, however, the Office continues to assert that simply because the authors report successful silencing when substituting uridine with 2'-deoxy-2'-fluoro uridine via enzymatic incorporation into a 742 nt long dsRNA molecule (resulting in ~25% modification), that the additional teachings of the authors in which silencing was abolished does nothing to teach away from, or in the alternative, does nothing to provide a high level of unpredictability, especially with respect to the application of more extensive combinations of modifications (~50% or greater) in *short interfering nucleic acid*. The Parrish et al. reference preceded the publication of the Elbashir et al. reference. Nevertheless, even in view of the prior work in long dsRNA, the Elbashir et al. authors still failed to apply "more extensive" modifications when attempting to optimize the stability and activity of siRNA and concluded that more extensive modification beyond the 3'-termini results in compromised RNAi activity in short interfering RNA (siRNA) molecules. In fact, Elbashir et al. specifically address the previous findings of Parrish et al., and provide detailed commentary on the effect of more extensive modifications to the siRNA duplex on RNAi activity (see Elbashir et al., page 6886).

The functional anatomy of long dsRNAs as a trigger for RNAi was analysed previously in C.elegans (Parrish et al., 2000). Activation of RNAi by injection of long dsRNA requires at least two steps: dsRNA processing by dicer RNase III and siRNP or RISC formation. Substitution of one of the strands of the long dsRNA by DNA abolished RNAi and even the substitution of C by dC or U by dT in only one of the strands caused a substantial decrease in RNAi. Because introduction of 2'-fluoro modifications into long RNA had no effect, it was suggested that an A-form double helical structure was important for triggering RNAi (Parrish et al., 2000). We have been able to substitute eight ribose residues of a siRNA duplex by 2'-deoxyribose residues without substantial reduction of RNAi, although it should be noted the 2'-deoxy modifications were clustered at the 3' end of the siRNAs, including the 2 nt 3' overhangs. It is possible that the four 2'-deoxy modifications, which are located in the paired region at the end of

the helix, do not affect the overall A-form helical structure and do not strongly compromise RISC formation. Complete modification of one or both siRNA strands by 2'-deoxyribose, however, abolished RNAi. Interestingly, substitution by 2'-O-methylribose, which adopts the ribose sugar pucker, also abolished RNAi, probably because methylation of the 2'-hydroxyls blocked hydrogen bond formation or introduced steric hindrance.

The above discussion, which addresses mechanistic concerns of modification beyond the 3'-overhang regions and the *unpredictable effects of such modification*, coupled with the plain language of "The siRNA user guide," which states that more extensive modification with 2'-deoxy and 2'-O-methyl beyond the 3'-overhangs results in reduced RNAi activity "probably by interfering with protein association for siRNP assembly," provides a strong teaching away and a high level of unpredictability with respect to more extensive modification of siRNA beyond the 3'-overhangs. Furthermore, any predictability based on known modification specific criteria, such as the ability to form an A-form helix, are destroyed by the lack of RNAi activity observed with 2'-O-methyl modifications. Parrish et al., which only provides one example of successful modification in *long* (742 base pair) RNA duplexes (with ~25% modification), but several examples of unsuccessful modification, does nothing to remedy the lack of predictability and ultimate teaching away provided by Elbashir with respect to *short* interfering RNA duplexes as instantly claimed. Taken together, the Elbashir and Parrish references provide a strong teaching away from, and such a high level of unpredictability, so as to preclude one of skill in the art (as demonstrated by the authors themselves) from arriving at or practicing the instantly claimed invention.

As discussed in the Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex (Notices), "[a] claimed combination of prior art elements may be nonobvious where the prior art teaches away from the claimed combination and the combination yields more than predictable results." Fed. Reg. 75:169 (September 1, 2010) page 53647 (citing *Crocs, Inc. v. U.S. Int'l Trade Comm'n.*, 598 F.3d 1294 (Fed. Cir. 2010)). The combination of features presently claimed, in view of the cited art that teaches against extensive modification of siRNA due to mechanistic concerns, ***would not yield a predictable result and, accordingly, one of skill in the art at the time of the invention would not have any reasonable expectation of success.***

Therefore, Applicant maintains that the Examiner's assertion that the instant invention is the result of "routine optimization" (Examiner's Answer, pages 14 and 21) is clearly erroneous and ignores the teachings away and unpredictability of the cited art with respect to extensive modification of siRNA that was evident at the time of the instant invention.

There is nothing in Nyce, Matulic-Adamic, Bertrand, Braasch, or Olie to remedy the shortcomings or teaching away that is evident in both Elbashir and Parrish. In fact, the Bertrand reference actually reinforces Applicant's position that one of skill in the art would not have been motivated to arrive at or would have had any reasonable expectation of success in practicing the instantly claimed invention. The Bertrand reference, which is the only other cited reference besides Elbashir et al. to even mention siRNA, provides a comparison of modified antisense and native siRNA with respect to inhibition of green fluorescent protein both *in vitro* and *in vivo*. The Office proposes that, after reading the Bertrand reference, one of skill in the art would have been motivated to incorporate the same modifications used in their antisense oligonucleotides into siRNA duplexes "for the same purpose of enhancing uptake of the molecule," especially considering the showing by Bertrand et al. that "siRNAs appear to be quantitatively more efficient with a longer lasting effect *in vitro* than antisense oligonucleotides." Examiner's Answer, page 10. However, the Office fails to truly appreciate that Bertrand et al. compared *modified* antisense to *unmodified* siRNA, finding that siRNAs *lacking* any stabilizing modifications appear to be quantitatively more efficient (i.e., with a longer lasting effect) than modified antisense oligonucleotides.

"A claimed compound would not have been obvious where there was not reason to modify the closest prior art lead compound to obtain the claimed compound and the prior art taught that modifying the lead compound would destroy its advantageous property." See Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex (Notices), Fed. Reg. 75:169 (September 1, 2010) page 53647 (citing *Eisai Co. Ltd. V. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353 (Fed. Cir. 2008)). Here, contrary to the Office's assertion that one of skill in the art would be motivated to incorporate additional modifications into the Elbashir duplex via "routine optimization,"

Applicant submits that in view of Bertrand, one of skill in the art would not have reason to apply more extensive modifications to the Elbashir duplex because: (1) siRNAs were shown by Bertrand et al. to be quantitatively more efficient (i.e., with a longer lasting effect) than modified antisense oligonucleotides, and (2) more extensive modifications would be expected to destroy this advantageous property. The proposition that one of skill in the art, armed with the teachings of Elbashir, Parrish, Matulic-Adamic, Bertrand, Braasch, and Olie, would be both motivated and have a reasonable expectation of success in arriving at the claimed invention simply cannot stand.

2. "Obvious to try" analysis fails to find obviousness

The Office continues to assert that "incorporating the modifications at various percentages in the double stranded nucleic acid molecules of Elbashir *et al.* is considered within the realm of routine optimization." Examiner's Answer, page 14. The Office states that "[a]rmed with not only the teachings of Elbashir et al., but the combined teachings of each of the instantly cited references, the skilled artisan would have been motivated to incorporate the modification in different combinations and locations within the duplex within the instant genus and would expect to result in active molecules." Examiner's Answer, page 26. With these conclusions, Applicant maintains that the Office appears to rely on hindsight in putting forth the proposition that sooner or later one of skill in the art would arrive at the instant invention by simply by testing various combinations of modifications and locations.

The Office is essentially arguing that the present invention would be "obvious to try" by using known modifications and routine experimentation and is therefore *prima facie* obvious. Applicant respectfully traverses. As recognized by the Office and as discussed in the Examination Guidelines Update: Developments in the Obviousness Inquiry After *KSR v. Teleflex* (Notices), Fed. Reg. 75:169 (September 1, 2010) page 53653, the Federal Circuit has clarified the standard for a finding of obviousness based on an "obvious to try" inquiry in *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009). Specifically, while acknowledging that, as stated by the U.S. Supreme Court in *KSR International Co. v Teleflex Inc.*, a skilled artisan, when motivated by an unmet need, can

look to combine elements within the scope of the prior art, the Federal Circuit held that it would be improper to hold a claim obvious when:

what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result; where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful

or

what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. In re Kubin, 561 F.3d 1351, 1359 (Fed. Cir. 2009)

To hold a claim obvious under these situations would be, according to the Federal Circuit, "succumb[ing] to hindsight claims of obviousness" and erroneous. *Id.* Reaffirming its prior holdings in *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988), the Federal Circuit explained that in order for an "obvious to try" inquiry to serve as the basis for obviousness, some direction in the prior art that would provide a reasonable expectation of success is still required. *See, O'Farrell*, at 903-04 and Fed. Reg. 75:169 (September 1, 2010) pages 53653-4. On the contrary, the combined teachings of the references cited against the pending claims do not provide guidance as to what individual modifications, when used "more extensively," will result in siRNA molecules that are both active and stable. In fact, the combined teachings actually indicate that more extensive incorporation of modifications into siRNA is detrimental and/or at least highly unpredictable based on the proposed mechanism of action, i.e. ***by interfering with protein association for siRNP assembly***. The prior art references, therefore, provide no guidance or any level of predictability that would lead one of skill in the art to conclude there was a reasonable expectation of success in combining the features presently claimed. Therefore, even an "obvious to try" inquiry fails to result in a finding of obviousness.

A reading of the cited prior art reveals a vast number of possible modifications that were available to one of skill in the art at the time of the instant invention. The

Office, in hindsight, attempts to oversimplify the criteria as being limited to only two choices, i.e. modification of purine vs. pyrimidine nucleotides, when stating that "the only positions that are specified are purines vs. pyrimidines, of which there are only two choices for the skilled artisan to incorporate modifications at." Examiner's Answer, page 26. Applicant respectfully traverses this oversimplification of the invention, as the claims do not simply specify purine vs. pyrimidine modifications, but rather require selections from at least *4 different criteria*: (1) the extent/number of modifications, i.e. 10 or more in each strand; (2) the types of modifications, i.e. 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, universal base, or phosphorothioate; (3) the positions of certain modifications, i.e. CAPs at the 3', 5', or both 3' and 5'-ends of the sense strand; and, (4) the type of nucleotide that is modified irrespective of its position within the duplex, i.e. 10 or more pyrimidine nucleotides. Therefore, the present invention could not have possibly arisen from routine optimization.

Even if one takes the position that routine testing with known modifications and known assays would *eventually* lead one of skill in the art to the presently claimed invention, this would be insufficient to establish a *prima facie* case of obviousness for at least two reasons. First, the references cited by the Office fail to give any indication of which parameters were critical to success, and in many instances taught away from the claimed modifications when applied more extensively. Second, at the time of the present invention, RNAi was a new technology and the experiences of the antisense/ribozyme arts at most gave general guidance as to the types of modifications one could apply to a siRNA molecule, providing merely a large selection of possibilities to choose from. These known modifications were individually demonstrated by those who first studied short dsRNA in the field to be sometimes feasible with limited application, but more often than not were incompatible with RNAi activity due mechanistic concerns, i.e., incompatibility with the siRNP protein machinery that is required to mediate RNAi. That unpredictability grows only larger if the known modifications were applied more extensively, and in combination, as is presently claimed. Thus, although numerous types of modifications were known in the art, this was not a case of testing a finite number of identified, predictable solutions. *"In such circumstances, where a defendant merely*

***throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness."* Kubin, at 1359.**

Therefore, this is not an instance where the prior art contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, ***and evidence suggesting that it would be successful.*** Rather, it is an instance where the prior art provides no direction as to which of many possible choices is likely to be successful and only general guidance as to the particular form of the claimed invention or how to achieve it. Most importantly (as addressed previously), the prior art, by teaching away from (or at least rendering highly unpredictable) more extensive modification beyond the 3'-termini, evidenced such a high level of unpredictability to preclude any reasonable expectation of success in practicing the claimed invention. Applicant's arguments do not rest on an absolute predictability of success, but rather point to a fundamental lacking of even a reasonable expectation of success. Any finding of obviousness under the "obvious to try" standard is therefore improper under the jurisprudence of *Kubin* and *O'Farrell*.

3. Secondary indicia preclude any finding of obviousness

Applicant maintains that no *prima facie* finding of obviousness can stand in view of the lack of motivation or any reasonable expectation of success that is evident from a plain reading of the cited art, and that even an "obvious to try" analysis fails because of the lack of guidance and/or predictability offered by the prior art. However, even if a *prima facie* showing of obviousness could be established, such a finding is effectively rebutted due to secondary considerations. As recognized by the Office, and as discussed in the Examination Guidelines Update: Developments in the Obviousness Inquiry After *KSR v. Teleflex (Notices)*,"[a]ll evidence, including evidence rebutting a *prima facie* case of obviousness, must be considered when properly presented." Fed. Reg. 75:169 (September 1, 2010) page 53657 (citing *In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007)). It is also well established that "evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." *Stratoflex, Inc. v. Aeroquip Corp*, 713 F.2d 1530, 1538 (Fed. Cir. 1983).

Secondary considerations include the failure of others and unexpected results. MPEP 716.01(a). Specifically, (1) the failure of others, coupled with (2) the surprising results obtained using the instant invention, are a clear and irrefutable demonstration of non-obviousness with respect to the presently claimed invention.

The instant invention provides double stranded nucleic acid molecules that are both highly serum stable and potent in mediating RNA interference, both *in vitro* and *in vivo*. The closest prior art is the Elbashir reference cited herein. It is important to recognize that the authors of Elbashir et al., armed with all of the knowledge proffered by the prior art with respect to chemical modification of nucleic acids (including the previous work published in the Parrish reference that was cited by and commented on by the authors of Elbashir et al., along with the prior teachings of Matulic-Adamic and Nyce), conducted extensive characterization and analysis of double stranded nucleic acid molecules with respect to optimized activity but *failed* in providing molecules that are both serum stable and active (see discussion *supra* and in more detail below with respect to **Figure 3** of the instant application and priority applications). Importantly, Elbashir et al. concluded that more extensive modifications beyond the 3'-termini were not favorable because of mechanistic concerns over the inability of such more extensively modified siRNA to interact with the RNAi protein machinery.

The instant invention is a departure from the teachings of Elbashir's '*The siRNA user guide*' and provides double stranded nucleic acid molecules having features that impart a high level of serum stability yet maintain significant, or even improved, RNAi activity compared to those of the prior art (see **Figures 3, 10, 11, 12, 13, 14, 15, 26, 29, 30, 39, 40, 41, 77, 80, 81, 82, 83, 84, 85, 86, and 87** and **Table I and IV** of the instant application, specific examples of which are described in greater detail below). These features are presently claimed. Specifically, Claims 52 and 59 require that the sense strand have 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modifications and a terminal cap moiety at the 3', 5' or both 3' and 5'-ends of the sense strand. Claims 52 and 59 also require that the antisense strand have 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modifications. In addition, Claim 52 requires modification of 10 or more pyrimidine nucleotides of the sense and antisense

strand with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro modifications. Claim 59 requires modification of 10 or more pyrimidine nucleotides of the sense or antisense strand with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro modifications. The dependent claims provide for additional modifications as well, including 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphorothioate modifications of the sense strand (Claims 54 and 60), and 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphorothioate modifications of the antisense strand (Claims 55 and 61). Dependent claims 57 and 63 specify 10 or more pyrimidines of the sense and antisense strand (Claim 57) or the sense or antisense strand (Claim 63) are 2'-O-methyl nucleotides. In this regard, even the minimal requirements of claims 52 and 59 differ substantially from the teachings of Elbashir et al. in terms of structure, and result in double stranded nucleic acid molecules with surprising and unexpected properties (as described below). Because dependent claims 57 and 63 specifically teach more extensive modification with 10 or more 2'-O-methyl modifications, which are taught by Elbashir to "block hydrogen bond formation or introduced steric hindrance," (Elbashir et al., page 6886) molecules of the invention having such modifications provide even more surprising results.

The Office asserts that "in the instant case applicant is not claiming any specific combination or modification schematic that produces an unexpected result, but is rather claiming a huge genus of possible molecules wherein molecules within the genus are certainly considered obvious in terms of the prior art" Examiner's Answer, page 25. Applicant respectfully disagrees with this highly conclusory characterization of the invention and maintains that the invention, when properly understood, is directed to a specific modification schematic that can be applied to any double stranded nucleic acid sequence as described in the specification, and which consistently provides unexpected results. For example, application of the features of claims 52 or 59 to any duplex sequence will result in a specific structure with well defined features that include: (1) the length of each strand; (2) the modification of 10 or more nucleotide positions with 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modifications and with caps at the 3', 5' or both 3' and 5'-ends of the sense strand; (3) the modification of 10 or more nucleotide positions with 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modifications of the antisense strand; and, (4) the modification of 10 or more pyrimidine

nucleotides of the sense *and* antisense strand with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides (claim 52) or 10 or more pyrimidine nucleotides of the sense *or* antisense strand modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides. Application of these features results in short interfering nucleic acid molecules having high serum stability coupled with a high level of activity/potency. These surprising and unexpected properties are described below with respect to numerous representative examples.

Examiners must consider comparative data in the specification which is intended to illustrate the claimed invention in reaching a conclusion with regard to the obviousness of the claims. *In re Margolis*, 785 F.2d 1029, 228 USPQ 940 (Fed. Cir. 1986). For example, inspection of **Figure 3** of the instant application shows a direct comparison of the state of the art at the time of the invention (modified Elbashir duplex, *see* Figure 4 on page 6882 of Elbashir *et al.*) to duplexes of the instant invention in terms of nuclease stability. The Elbashir duplex, having 3'-terminal 2'-deoxy modifications (SEQ ID NOs: 394 and 395), when tested in human serum, has a half life ($T_{1/2}$) of *15 seconds*. The duplexes of the instant invention however, all having the features claimed, i.e., 10 or more enumerated modifications in each strand with terminal cap(s) and with 10 or more of the enumerated pyrimidine modifications, all show dramatically improved nuclease stability: $T_{1/2}$ of *138 minutes* for SEQ ID NOs: 396 and 397; $T_{1/2}$ of *3.7 days* for SEQ ID NOs: 396 and 398; $T_{1/2}$ of *72 minutes* for SEQ ID NOs: 396 and 399; $T_{1/2}$ of *40 days* for SEQ ID NOs: 396 and 400; and $T_{1/2}$ of *32 days* for SEQ ID NOs: 396 and 401.

The Office alleges that "[a]pplicant is pointing to species that are not representative of the instant genus and do not represent unexpected results for the instant genus". Examiner's Answer, page 26. In response, Applicant asserts that the numerous examples of sequences incorporating the claimed features that show surprising and unexpected results are sufficient to accurately represent the scope of the claims. The RNAi activity of numerous representative examples of short interfering nucleic acid duplexes having 10 or more of the enumerated modifications (2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base) in both the sense strand and antisense strand, 3', 5', or both 3' and 5' caps of the sense strand, and 10 or more 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro pyrimidine modifications in the sense and/or antisense strand, have

comparable to or even improved RNAi activity when compared to a representative control duplex of the prior art. See for example **Figure 14**, in which the siGL2 control (Elbashir duplex) is compared to various duplexes of the invention having a "Stab 6" (see Table IV) sense strand (sequence 30222, SEQ ID NO: 373) consisting of 3' and 5'-terminal caps with 2'-O-methyl and 2'-deoxy pyrimidine modifications and various "Stab 5" (Table IV) antisense strands, all having 2'-deoxy-2'-fluoro and 2'-deoxy pyrimidine modifications (sequence 30546, SEQ ID NO: 386; sequence 30224, SEQ ID NO: 374; sequence 30551, SEQ ID NO: 387; sequence 30557, SEQ ID NO: 388, and sequence 30558, SEQ ID NO: 389). Also, see for example **Figure 15**, in which the siGL2 control (Elbashir duplex) is compared to duplexes of the invention having a "Stab 4", "Stab 8" or "Stab 7" (Table IV) sense strand (sequence 30063, SEQ ID NO: 372; sequence 30434, SEQ ID NO: 384; and sequence 30435, SEQ ID NO: 385 respectively) all consisting of 3' and 5'-terminal caps with 2'-deoxy, 2'-deoxy-2'-fluoro or 2'-O-methyl pyrimidine modifications and a "Stab 8" (Table IV) antisense strand having 2'-deoxy-2'-fluoro pyrimidine and phosphorothioate modifications (sequence 30430, SEQ ID NO: 375). As shown in these figures, the activity of the serum stable double stranded nucleic acid molecules of the invention is an *unexpected finding* in view of the teachings of the closest prior art.

The Office states that "[t]he comparison set forth by applicant is comparing one specific duplex of Elbashir, which is not demonstrative of any target sequence or even selection of the position of the modifications within the duplex of Elbashir et al." Examiner's Answer, page 29. The Office further states that "Elbashir et al. concentrated on the terminal regions of the siRNA duplex and simply offers motivation to test for incorporation of modifications at other positions." Examiner's Answer, page 29. Applicant respectfully disagrees. First, as demonstrated above, Elbashir did not concentrate on the "terminal regions" of the siRNA duplex, only the 3'-terminal region was shown to tolerate modification, and only with 2'-deoxy nucleotides. Second, the teaching away and lack of predictability with respect to modification beyond the 3'-terminal regions would not provide motivation to test for incorporation of modifications at other positions. Finally, Applicant has shown surprising and unexpected results of numerous representative examples (such as described above in **Figures 3, 14 and 15**) of

different modified sequences that are representative of the claimed genus, not just one example. All of these examples have extensive modification of pyrimidine nucleotides, use of terminal cap modifications, and all have ~50% or greater modification of each strand (i.e., 10 or more of the enumerated modifications as claimed) to impart highly stable siRNA molecules that have unexpectedly robust RNAi activity.

The unexpected results, contrary to the teaching of the prior art are also clearly exemplified in additional representative examples in **Figures 28, 29, and 30**, in which the RNAi activity of various duplexes of the invention (Stab 4/5; Stab 7/8, and Stab 7/11 respectively, all having sense strands with 3' and 5'-terminal caps combined with 2'-deoxy and 2'-deoxy-2'-fluoro pyrimidine modifications with ribonucleotide (Stab 4, Table IV) or 2'-deoxy (Stab 7, Table IV) purines and antisense strands having 2'-deoxy and 2'-deoxy-2'-fluoro pyrimidine modifications with phosphorothioate modifications and with ribonucleotide (Stab 5, Table IV), 2'-O-methyl (Stab 8, Table IV) or 2'-deoxy (Stab 11, Table IV) purines) are compared to an all RNA duplex control in inhibiting HBV gene expression in a dose response time course study (note, all sequences for the constructs in **Figures 28, 29, and 30** are all described in **Table I**). As shown in **Figures 28, 29, and 30**, the extensively modified duplexes of the invention all show comparable activity to the all RNA control at day 3, and *improved* activity at day 6 and day 9 time points.

As is clearly shown in **Figures 3, 14, 15, 28, 29, and 30** (amongst others), *the double stranded nucleic acid molecules of the invention are significantly more stable than the double stranded nucleic acid molecules of the prior art, and surprisingly have retained or improved activity over the prior art molecules that allow these molecules to function as therapeutic modalities.* (Emphasis added) Applicant reiterates that a claimed combination of prior art elements may be nonobvious where the prior art teaches away from the claimed combination and the combination yields more than predictable results. *Crocs, Inc. v. U.S. Int'l Trade Comm'n.*, 598 F.3d 1294 (Fed. Cir. 2010) The chemically modified duplexes of the instant invention are a significant and inventive advancement over the teachings of the closest prior art Elbashir reference, who teach that "more extensive" modification beyond the 3'-termini is detrimental to RNAi activity on mechanistic grounds because of impaired association with the RNAi protein machinery,

and whose attempts to more extensively modify such molecules resulted in *abolished* activity. Thus, even if the Office were able to make a *prima facie* showing of obviousness (which is not the case), the failure of others combined with the surprising, unpredictable, and unexpected results as taught by the application as filed and the priority documents, unequivocally preclude any finding of obviousness.

II. There is no obviousness-type double patenting issue over Applicant's USSN 12/170,290; 12/185,652; 12/204,572; 12/203,055; 12/200,736; 12/203,731; 12/204,612; 12/175,367; and 10/444,853 applications

The Office provisionally rejected claims 52-56 as allegedly being unpatentable on the ground of non-statutory obviousness-type double patenting over claims 1-20 of co-pending Application No. 12/170,290 (now US patent No. 7,662,951); claims 1-20 of co-pending Application No. 12/185,652; claims 1-20 of co-pending Application No. 12/204,572 (now US patent No. 7,678,897); claims 1-20 of co-pending Application No. 12/203,055 (now US patent No. 7,700,760); claims 1-20 of co-pending Application No. 12/200,736; claims 1-20 of co-pending Application No. 12/203,731 (now US patent No. 7,659,390); claims 1-20 of co-pending Application No. 12/204,612 (now US patent No. 7,667,030); claims 1-20 of co-pending Application No. 12/175,367 (now US patent No. 7,795,422); and claims 129-138 of co-pending Application No. 10/444,853. Office Action, at pages 24-28.

Applicant respectfully submits that terminal disclaimers in accordance with § 1.321(c) have been filed in each of 10/444,853, 12/185,652, 12/200,736, 12/170,290 (now US patent No. 7,662,951); and 12/175,367 (now US patent No. 7,795,422) over the instant 10/720,448 application, thus rendering the provisional obviousness-type double patenting rejections moot with respect to these patents or patent applications (see Appendix B).

With respect to Application Nos. 12/204,572 (now US patent No. 7,678,897); 12/203,055 (now US patent No. 7,700,760); 12/203,731 (now US patent No. 7,659,390); and 12/204,612 (now US patent No. 7,667,030), Applicant respectfully traverses the obviousness-type double patenting rejections. Each of these patents/applications were later filed relative to the instant application and have issued claims directed to an

invention that is patentably distinct from the instant invention and which could not have been included in the instant application.

The Office alleges that: "With regards to the claim sets that are directed to specific targets, these species anticipate the instantly claimed broad genus that is not directed to any specific target. Furthermore, the instant claims specify pyrimidine modifications and therefore the claims of the conflicting applications and the instant claims are directed to overlapping subject matter. The instant claims embrace the modifications required by the conflicting applications." Examiner's Answer, page 30. Applicant respectfully traverses because the appropriate standard in evaluating the remaining obviousness-type double patenting rejections is with a two-way test as opposed to a one-way test. "If the patent is the later filed application, the question of whether the timewise extension of the right to exclude granted by a patent is justified or unjustified must be addressed. A two-way test is to be applied only when the applicant could not have filed the claims in a single application and there is administrative delay." MPEP § 804, citing *In re Berg*, 46 USPQ2d 1226 (Fed. Cir. 1998).

Here, each of 12/204,572 (now US patent No. 7,678,897); 12/203,055 (now US patent No. 7,700,760); 12/203,731 (now US patent No. 7,659,390); and 12/204,612 (now US patent No. 7,667,030) are later filed applications and have claims drawn to nucleic acid molecules having specific sequence identification number (SEQ ID NO) limitations that are patentably distinct from the instant claims. All of these issued claims recite specific SEQ ID NOs that are not disclosed in the instant application or any of the priority documents, and therefore could not have been included in the instant application. Furthermore, as is evident in the file wrapper, significant administrative delay by the Office exists with respect to the handling of the instant application. Because the two way test applies, and because the above cited patents all have patentably distinct claims, Applicant respectfully requests withdrawal of these provisional rejections. If however, the Board feels that these obviousness-type double patenting rejections are proper, then Applicant will file one or more terminal disclaimers to address any standing rejections that may be deemed proper.

III. Conclusions

The instant claims are patentable. Applicant therefore respectfully requests withdrawal of the standing rejections and allowance of the claims.

Respectfully submitted,

Date: December 15, 2010

By: **Peter Haerberli**

Peter Haerberli
Reg. No. 52,980
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APPENDIX A

CLAIMS ON APPEAL

1-51. (Canceled)

52. (Previously presented) A short interfering RNA (siRNA) molecule having a sense strand and an antisense strand that mediates RNA interference, wherein:

(a) each strand is between 18 and 24 nucleotides in length;

(b) the sense strand comprises 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides, and a terminal cap molecule at the 3'-end, the 5'-end, or both 3' and 5'-ends of the sense strand;

(c) the antisense strand comprises 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides; and

(d) 10 or more pyrimidine nucleotides of the sense and antisense strand are 2'-deoxy, 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotides.

53. (Canceled)

54. (Previously presented) The siRNA molecule of claim 52, wherein the sense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 phosphorothioate internucleotide linkages.

55. (Previously presented) The siRNA molecule of claim 52, wherein the antisense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 phosphorothioate internucleotide linkages.

56. (Previously presented) A composition comprising the siRNA molecule of claim 52 and a pharmaceutically acceptable carrier or diluent.

57. (Previously presented) The siRNA molecule of claim 52, wherein 10 or more pyrimidine nucleotides of the sense and antisense strand are 2'-O-methyl nucleotides.

58. (Previously presented) The siRNA molecule of claim 52, wherein 10 or more pyrimidine nucleotides of the sense and antisense strand are 2'-deoxy-2'-fluoro nucleotides.

59. (Previously presented) A short interfering RNA (siRNA) molecule having a sense strand and an antisense strand that mediates RNA interference, wherein:
- (a) each strand is between 18 and 24 nucleotides in length;
 - (b) the sense strand comprises 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides, and a terminal cap molecule at the 3'-end, the 5'-end, or both 3' and 5'-ends of the sense strand;
 - (c) the antisense strand comprises 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides; and
 - (d) 10 or more pyrimidine nucleotides of the sense or antisense strand are 2'-deoxy, 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotides.
60. (Previously presented) The siRNA molecule of claim 59, wherein the sense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 phosphorothioate internucleotide linkages.
61. (Previously presented) The siRNA molecule of claim 59, wherein the antisense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 phosphorothioate internucleotide linkages.
62. (Previously presented) A composition comprising the siRNA molecule of claim 59 and a pharmaceutically acceptable carrier or diluent.
63. (Previously presented) The siRNA molecule of claim 59, wherein 10 or more pyrimidine nucleotides of the sense or antisense strand are 2'-O-methyl nucleotides.
64. (Previously presented) The siRNA molecule of claim 59, wherein 10 or more pyrimidine nucleotides of the sense or antisense strand are 2'-deoxy-2'-fluoro nucleotides.

APPENDIX B

EVIDENCE APPENDIX

See attached terminal disclaimers filed in accordance with § 1.321(c) for each of Application Nos. 10/444,853, 12/185,652, 12/200,736, 12/170,290 (now US patent No. 7,662,951); and 12/175,367 (now US patent No. 7,795,422).

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

**TERMINAL DISCLAIMER TO OBTAIN A PROVISIONAL DOUBLE PATENTING
REJECTION OVER A PENDING "REFERENCE" APPLICATION**

Docket Number (Optional)

SIR-MIS-00001-US-CIP

In re Application of: Beigelman et al.

Application No.: 10/444,853

Filed: 05/23/2003

For: RNA Interference Mediated inhibition of Gene Expression Using Chemically Modified Short Interfering Nucleic Acid (siNA)

The owner*, Sima Therapeutics, Inc., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number 10/720,448, filed on 11/24/2003, as such term is defined in 35 U.S.C. 154 and 173, and as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that: any such patent: granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 52,980

/Peter Haeberli/

Signature

December 14, 2010

Date

Peter Haeberli

Typed or printed name

415.814.8491

Telephone Number

- ☒ Terminal disclaimer fee under 37 CFR 1.20(d) is included.

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*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).

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This collection of information is required by 37 CFR 1.321. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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**TERMINAL DISCLAIMER TO OBTAIN A PROVISIONAL DOUBLE PATENTING
REJECTION OVER A PENDING "REFERENCE" APPLICATION**Docket Number (Optional)
SIR-MIS-00047-US-CNT

In re Application of: McSwiggen et al.

Application No.: 12/185,652

Filed: August 4, 2008

For: RNA INTERFERENCE MEDIATED INHIBITION OF FOS GENE EXPRESSION USING SHORT INTERFERING NUCLEIC ACID (siNA)

The owner*, Sirna Therapeutics, Inc., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number 10/720,448, filed on 11/24/2003, as such term is defined in 35 U.S.C. 154 and 173, and as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that: any such patent: granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 51,737

/Laura M. Ginkel, Reg. # 51,737/
Signature

November 19, 2010
Date

Laura M. Ginkel
Typed or printed name

732-594-1932
Telephone Number

- ☒ Terminal disclaimer fee under 37 CFR 1.20(d) is included.

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**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING
REJECTION OVER A PENDING "REFERENCE" APPLICATION**Docket Number (Optional)
SIR-MIS-00041-US-CNT

In re Application of: Beigelman et al.

Application No.: 12/200,736

Filed: 08/28/2008

For: RNA Interference Mediated Inhibition of Cyclin D1 Gene Expression Using Short Interfering Nucleic Acid (siNA)

The owner*, Merck Sharp & Dohme Corp., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number 10/720,448, filed on 11/24/2003, as such term is defined in 35 U.S.C. 154 and 173, and as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

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2. ☒ The undersigned is an attorney or agent of record. Reg. No. 43,166

/Elaine C. Stracker/

Signature

December 14, 2010

Date

Elaine Stracker

Typed or printed name

415.814.8468

Telephone Number

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REJECTION OVER A PENDING "REFERENCE" APPLICATION**

Docket Number (Optional)

SIR-MIS-00007-US-CNT[3]

In re Application of: Beigelman et al.

Application No.: 12/170,290 issued 2/16/10 as U.S. Patent 7,662,951

Filed: 07/09/2008

For: RNA INTERFERENCE MEDIATED TREATMENT OF ALZHEIMER'S DISEASE USING SHORT INTERFERING NUCLEIC ACID (siNA)

The owner*, Sima Therapeutics, Inc., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number 10/720,448, filed on 11/24/2003, as such term is defined in 35 U.S.C. 154 and 173, and as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

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2. ☒ The undersigned is an attorney or agent of record. Reg. No. 43,168

/Elaine C. Stracker/

Signature

December 14, 2010

Date

Elaine Stracker

Typed or printed name

415.814.8468

Telephone Number

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Docket Number (Optional)

SIR-MIS-00052-US-CNT

In re Application of: Belgelman et al.

Application No.: 12/175,367 issued 09/14/10 as U.S. Patent 7,795,422

Filed: 07/17/2008

For: RNA INTERFERENCE MEDIATED INHIBITION OF HYPOXIA INDUCIBLE FACTOR 1 (HIF1) GENE EXPRESSION USING SHORT INTERFERING NUCLEIC ACID (siNA)

The owner*, Merck Sharp & Dohme Corp., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number 10/720,448 filed on 11/24/2003, as such term is defined in 35 U.S.C. 154 and 173, and as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

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2. ☒ The undersigned is an attorney or agent of record. Reg. No. 43,166

/Elaine C. Stracker/

Signature

12/14/10

Date

Elaine Stracker

Typed or printed name

415.814.8468

Telephone Number

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APPENDIX C

RELATED PROCEEDINGS APPENDIX

See attached decision for Appeal No. 2009-2562, resulting from application No. 90/008,177 (Re-examination of US Patent 7,022,828).



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/008,177	08/22/2006	7022828	01-664C/400.050	9670
79693	7590	05/26/2009		
Sirna Therapeutics, Inc. 1700 Owens Street 4th Floor San Francisco, CA 94158			EXAMINER PONNALURI, PADMASHRI	
			ART UNIT 3991	PAPER NUMBER
			MAIL DATE 05/26/2009	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte SIMA THERAPEUTICS, INC.,
Patent Owner and Appellant

Appeal 2009-002562
Reexamination Control 90/008,177
Patent 7,022,828
Technology Center 3900

Decided:¹ May 26, 2009

Before CAROL A. SPIEGEL, ROMULO H. DELMENDO, and
JEFFREY FREDMAN, *Administrative Patent Judges*.

SPIEGEL, *Administrative Patent Judge*.

DECISION ON APPEAL

I. Statement of the Case

Appellant appeals under 35 U.S.C. §§ 134(b) and 306 from an Examiner's final rejection of all pending claims, claims 1-9 and 14-16.² We have jurisdiction under 35 U.S.C. §§ 134(b) and 306. We AFFIRM.

¹ The two-month for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

The subject matter on appeal is directed to a double stranded ("ds") siRNA molecule that down regulates expression of an IKK- γ gene and which has been modified with at least one 2'-O-methyl group and at least one 2'-fluoro group to protect the siRNA from nuclease degradation. Each strand of the siRNA is about 18 to about 28 nucleotides ("nt") in length.

Claims 1, 3, 4, and 7 are illustrative and read (App. Br.³ 25-26):

1. A chemically modified double stranded siRNA molecule that down regulates expression of an IKK-gamma gene via RNA interference (RNAi), wherein: a) each strand of said siRNA molecule is independently about 18 to about 28 molecules in length; b) one strand of said siRNA molecule comprises nucleotide sequence having sufficient complementarity to an RNA of said IKK-gamma gene for the siRNA to direct cleavage of said RNA via RNA interference; and (c) wherein said siRNA molecule comprises 2'-O-methyl and 2'-fluoro modifications.

3. The siRNA molecule of claim 1, wherein said siRNA molecule is assembled from two separate oligonucleotide fragments wherein a first fragment comprise the sense strand and a second fragment comprises the antisense strand of said siRNA molecule.

4. The siRNA molecule of claim 3, wherein said sense strand is connected to the antisense strand via a linker molecule.

² Appellant cancelled claim 13 in its Reply Brief under 37 C.F.R. § 41.41 filed 5 September 2008 ("Reply Br."), as acknowledged by the Examiner in a miscellaneous communication mailed 17 September 2008.

³ Supplemental Brief on Appeal filed 13 June 2008 ("App. Br.").

7. The siRNA molecule of claim 3, wherein said second fragment comprises a terminal cap moiety at a 5'-end, a 3'-end, or both of the 5' and 3' ends of said second strand.

The Examiner has rejected

- (A) claims 1-3, 14, and 16 under 35 U.S.C. § 103(a) as unpatentable over Tuschl I⁴ and Tuschl II⁵ in view of Yamaoka,⁶ Smahi,⁷ and Krappmann⁸ (Ans.⁹ 5-8);
- (B) claims 4-6 under 35 U.S.C. § 103(a) as unpatentable over Tuschl I, Tuschl II, Yamaoka, Smahi, and Krappmann taken further in view of Agrawal¹⁰ (Ans. 8);

⁴ Published Patent Application US 2002/0086356 A1, *RNA Sequence-Specific Mediators of RNA Interference*, published 4 July 2002, based on application 09/821,832, filed 30 March 2001, by Tuschl et al. ("Tuschl I").

⁵ International Publication WO 02/44321 A2, *RNA Interference Mediating RNA Small RNA Molecules*, published 6 June 2002, based on international application PCT/EP01/13968, filed 29 November 2001, by Tuschl et al., which claims priority benefit of US provisional application 60/279,661, filed 30 March 2001 ("Tuschl II").

⁶ Yamaoka et al., "Complementation Cloning of NEMO, a Component of the I κ B Kinase Complex Essential for NF- κ B Activation," *Cell*, 93 (26 June 1998): 1231-1240 ("Yamaoka").

⁷ Smahi et al., "Genomic Rearrangement in *NEMO* impairs NF- κ B activation and is the cause of incontinentia pigmenti," *Nature*, 405 (25 May 2000):466-472 ("Smahi").

⁸ Krappmann et al., "The I κ B Kinase (IKK) Complex is Tripartite and Contains IKK γ but not IKAP as a Regular Component," *The Journal of Biological Chemistry*, 275 (22 September 2000):29779-29787 ("Krappmann").

⁹ Examiner's Answer mailed 7 July 2008 ("Ans.").

¹⁰ International Publication WO 94/01550, *Self-Stabilized Oligonucleotides as Therapeutic Agents*, published 20 January 1994, based on international

- (C) claims 7 and 8 under 35 U.S.C. § 103(a) as unpatentable over Tuschl I, Tuschl II, Yamaoka, Smahi, and Krappmann taken further in view of Matulic-Adamic¹¹ (Ans. 9);
- (D) claims 1-3 under 35 U.S.C. § 103(a) as unpatentable over Kenwick¹² in view of Tuschl I and Tuschl II (Ans. 9-11);
- (E) claims 1-3 and 14-16 under 35 U.S.C. § 103(a) as unpatentable over Elbashir,¹³ Tuschl II, and Bass¹⁴ in view of Yamaoka, Krappmann, and Smahi (Ans. 11-14);
- (F) claims 4-6 under 35 U.S.C. § 103(a) as unpatentable over Elbashir, Tuschl II, Bass, Yamaoka, Krappmann, and Smahi further in view of Agrawal (Ans. 14-15);
- (G) claims 7-8 under 35 U.S.C. § 103(a) as unpatentable over Elbashir, Tuschl II, Bass, Yamaoka, Krappmann, and Smahi further in view of Matulic-Adamic (Ans. 15);

application PCT/US93/06326, filed 2 July 1993, by Agrawal et al. ("Agrawal").

¹¹ US Patent 5,988,203, *Enzymatic Nucleic Acids Containing 5'- and/or 3'Cap Structures*, issued 7 December 1999, to Matulic-Adamic et al. ("Matulic-Adamic").

¹² US Patent 6,824,972 B2, *Diagnosis and Treatment of Medical Conditions Associated with Defective NF κ B (NF- κ B) Activation*, issued 30 November 2004, based on application 09/863,049, filed 22 May 2001, to the Kenwick et al. ("Kenwick").

¹³ Elbashir et al., "Duplexes of 21-nucleotide RNAs mediate RNA interference in cultured mammalian cells," *Nature*, 411 (24 May 2001):494-498 ("Elbashir").

¹⁴ B. Bass, "The short answer," *Nature*, 411 (24 May 2001):428-429 ("Bass").

- (H) claims 1-3, 9, and 14-16 under 35 U.S.C. § 103(a) as unpatentable over Fire¹⁵ and Tuschl II in view of Yamaoka, Krappmann, and Smahi (Ans. 16-18);
- (I) claims 4-6 under 35 U.S.C. § 103(a) as unpatentable over Fire, Tuschl II, Yamaoka, Krappmann, and Smahi further in view of Agrawal (Ans. 18-19); and,
- (J) claims 7-8 under 35 U.S.C. § 103(a) as unpatentable over Fire, Tuschl II, Yamaoka, Krappmann, and Smahi further in view of Matulic-Adamic (Ans. 19-20).¹⁶

The rejections fall into two groups. In the first group, the Examiner relies on (a) Tuschl I, Elbashir, or Fire as teaching sequence-specific inhibition of gene expression by dsRNA (RNA interference or "RNAi"), specifically by siRNA, (b) Tuschl II as teaching 19-21 nucleotide siRNA wherein the 2' OH group of a ribose is replaced by an OR, wherein R is C₁₋₆ alkyl, or a fluoro to improve stability, (c) Yamaoka as teaching the cDNA sequence of an IKK- γ gene, and (d) Krappmann and Smahi each as teaching the relationship between the IKK- κ gene and NF- κ B activation. The Examiner further relies on Agrawal and Matulic-Adamic as teaching additional methods of improving the stability of RNA strands from degradation by nucleases. In the second group, the Examiner relies on Kenwrick as teaching methods of treating NF- κ B related medical conditions

¹⁵ US Patent 6,506,559 B1, *Genetic Inhibition by Double-Stranded RNA*, issued 14 July 2003, based on application 09/215,257, to Fire et al. ("Fire").

¹⁶ The Examiner withdrew the rejection of claims 1-9 and 13-16 under 35 U.S.C. §§ 112, first paragraph (written description), and 305 (enlarging the scope of the claimed invention) (Ans. 2-3). Cancellation of claim 13 renders its rejections under 35 U.S.C. § 103(a) moot.

with sequences 100% complementary to an IKK- γ gene and Tuschl I and II as teaching the use of modified siRNA to block mRNA translation *in vivo*.

Appellant argues that the Examiner has failed to give any reason for providing 2'-O-methyl *and* 2'-fluoro modifications on the same siRNA, especially since Tuschl II is alleged to teach avoiding 2'-O-methyl modifications of the siRNA. Appellant further argues that Yamaoka fails to disclose the cDNA sequence encoding an IKK- γ gene and that the Examiner has failed to provide any reason for down regulating IKK- γ gene expression. Appellant finally argues that the teachings of Agrawal and Matulic-Adamic are directed to antisense and ribozyme interference RNA technology, respectively, and therefore are irrelevant to siRNA interference technology.

At issue is whether Appellant has shown the Examiner reversibly erred in (i) finding that Yamaoka disclosed the cDNA sequence of an IKK- γ gene, (ii) concluding that an ordinarily skilled artisan would have had both a motivation to and a reasonable expectation of success of providing an siRNA molecule with at least one 2'-O-methyl group and at least one 2'-fluoro group, (iii) failing to provide a reason for down regulating an IKK- γ gene, (iv) concluding that it would have been obvious to join a sense and an anti-sense RNA strand into a single ds siRNA via a linker molecule based on the teachings of Agrawal, (v) concluding that it would have been obvious to cap either or both ends of the antisense strand based on the teachings of Matulic-Adamic, and (vi) concluding that Kenwrick provided a teaching or suggestion of down regulating IKK- γ gene expression.

Since Appellant has provided separate patentability arguments for claim groupings 4-6 and 7-8, we decide this appeal on the basis of claims 1,

4 and 8. 37 C.F.R. § 41.37(c)(1)(vii). We also note that the Evidence Appendix of the principal brief does not cite to or provide any evidence being relied upon by Appellant in this appeal. 37 C.F.R. § 41.37(c)(2)(ix).

II. Findings of Fact ("FF")

The following findings of fact are supported by a preponderance of the evidence of record.

A. RNA interference

- [1] The central dogma of molecular biology comprises three processes: replication (the copying of parental DNA to form daughter DNA molecules with identical nucleotide sequences), transcription (the process by which parts of the genetic message encoded in DNA are precisely copied into RNA), and translation (whereby the genetic message encoded in messenger RNA ("mRNA") is translated, i.e., expressed, into a protein with a particular amino acid sequence) (see e.g., Lehninger¹⁷ 921-922).
- [2] As stated by Bass, "[o]ne way of seeing what a gene does is to block its messenger RNA and note the effects" (Bass abstract).
- [3] Several strategies can be used to achieve gene-specific inhibition, including single strand nucleic acid mediated antisense¹⁸ technology and dsRNA mediated RNA interference (Fire 1: 63-67; 4:20-28).
- [4] RNA interference ("RNAi") is a cellular process by which a dsRNA sequence-specifically blocks the expression of a gene (Fire 1:17-19;

¹⁷ Lehninger PRINCIPLES OF BIOCHEMISTRY, fourth edition, W.H. Freeman and Company, New York (2005) ("Lehninger") (copy enclosed).

¹⁸ Antisense technology involves a single stranded antisense oligonucleotide pairing with its complementary mRNA to block translation (Fire 1:63-2:20).

Tuschl I ¶3; Bass 428, col. 1, ¶2; Elbashir 494 abstract; Tuschl II 1:11-26).

- [5] According to Fire "dsRNA is at least 100-fold more effective than ... antisense RNA in reducing gene expression" (Fire 3:30-32).
- [6] Similarly, according to Tuschl I and Elbashir, "siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments" (Tuschl I ¶148; Elbashir p. 496, col. 1, ¶2).
- [7] According to Fire, the dsRNA (i) may be formed by a single self-complementary RNA strand or two complementary RNA strands (i.e., sense and antisense strands), (ii) preferably contains a nucleotide sequence greater than 90% identical to a portion of the gene being targeted for inhibition, (iii) may include modifications to the phosphate-sugar backbone or the nucleoside, and (iv) is at least 25 base pairs long (Fire 4:41-46; 7:31-32, 42-44, 53-54, 64-67; 26:55-59 (claim 10)).
- [8] According to Fire, the dsRNA may be used to inhibit expression of a gene associated with disease causation or symptoms or to identify gene function in an organism (Fire 9:65-10:7; 10:26-28; 12:17-20).
- [9] According to Tuschl I,

RNAi is envisioned to begin with cleavage of the dsRNA to 21-23 nt products by a dsRNA-specific nuclease ... These short dsRNAs might then be dissociated with an ATP-dependent helicase ... to 21-23 nt asRNAs [i.e., antisense RNAs] that could then target the mRNA for cleavage. The short asRNAs are imagined to remain associated with the RNAi-specific proteins ... originally bound by

the full-length dsRNA ... Finally, a nuclease ...
would cleave the mRNA. [Tuschl I ¶36.]

- [10] Thus, Tuschl I is directed 21-23 nt dsRNA molecules useful as sequence-specific mediators of RNAi to inhibit mRNAs that encode proteins associated with or causative of a disease or an undesirable condition (Tuschl I ¶57).
- [11] In other words, according to Tuschl I, if the sequence of the gene to be targeted is known, any dsRNA can be used to mediate RNAi provided that it has sufficient homology to the targeted gene (Tuschl I ¶¶ 57, 59).
- [12] Tuschl I also showed that 21 nt siRNA duplexes were able to specifically inhibit a target gene expression without activating an interferon response (Tuschl I ¶144).
- [13] A preferred embodiment of Tuschl I comprises 21 nt strands with 2 nt overhangs at both 3' ends of the RNA, wherein the 3' overhangs can be modified, e.g., by 2' (deoxy) thymidine substitution, to enhance the stability of the siRNA (Tuschl I ¶¶55, 148).
- [14] According to Tuschl I, the absence of a 2' OH group enhances the nuclease resistance of the 3' overhang *in vitro* (Tuschl I ¶55).
- [15] Elbashir showed that 21 and 22 nt siRNA duplexes mediated sequence-specific mRNA degradation, without activating the interferon system as do dsRNAs having more than 30 base paired nucleotides (Elbashir abstract; p. 495, col. 1, ¶2; p. 496, col. 1, ¶3).
- [16] Specifically, Elbashir synthesized 21-nt siRNA duplexes comprising sense and antisense strands with 2-nt 3' overhangs comprising 2' (deoxy) thymidine because the thymidine overhang reduces the cost

of RNA synthesis and may enhance the nuclease resistance of the siRNA (¶ bridging pp. 495-496; Figure 1).¹⁹

[17] According to Bass, although RNAi is routine in laboratories to study a wide range of organisms, Tuschl (explicitly referring to Elbashir) describes research that paves the way for successful RNAi use in mammalian cells, namely that siRNAs shorter than about 30 bps mediate a sequence-specific response whereas longer dsRNAs mediate a global, nonspecific response (Bass, p. 428; Figure 1).

B. RNA strand modifications

[18] Tuschl II discloses 19-25 nt siRNA duplexes capable of mediating RNAi and/or DNA methylation, wherein the most effective dsRNAs comprise two 21 nt strands which base paired such that 1-3, especially 2 nt 3' overhangs are present on both ends of the dsRNA (Tuschl II 3:18-24; 4:18-21).

[19] According to Tuschl II,

[t]he target RNA cleavage reaction guided by siRNAs is highly sequence-specific. However, not all positions of a siRNA contribute equally to target recognition. Mismatches in the center of the siRNA duplex are most critical and essentially abolish target RNA cleavage. In contrast, the 3' nucleotide of the siRNA strand (e.g., position 21) that is complementary to the single-stranded target

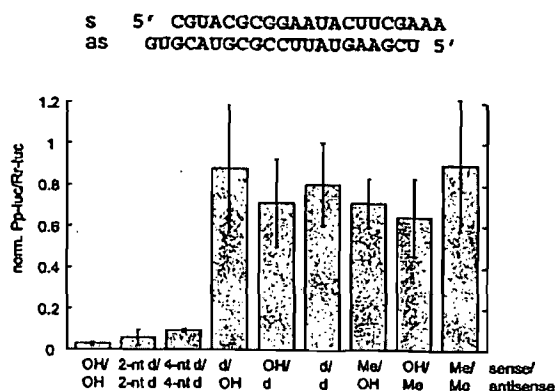
¹⁹ DNA and RNA differ in three main ways. First, RNA is usually a single-stranded molecule in most of its biological roles, whereas DNA is usually double-stranded. Second, RNA contains a ribose sugar, whereas DNA contains a deoxyribose sugar (i.e., deoxyribose does not have an OH group attached to the 2' position of the sugar ring). Third, the complementary base to adenine in RNA is uracil, not thymine as it is in DNA.

RNA, does not contribute to specificity of the target recognition. Further, the sequence of the unpaired 2-nt 3' overhang of the siRNA strand with the same polarity as the target RNA is not critical for target RNA cleavage as only the antisense siRNA strand guides target recognition. Thus, from the single-stranded overhanging nucleotides only the penultimate position of the antisense siRNA (e.g., position 20) needs to match the targeted sense mRNA. [Tuschl II 4:23-5:2.]

- [20] In other words, according to Tuschl II, the cleavage sites for both sense and antisense target RNAs are located in the middle of the region spanned by the siRNA duplexes (Tuschl II 47:4-5).
- [21] Tuschl II discloses stabilizing the 3' overhangs against degradation to enhance *in vivo* and *in vitro* stability of the siRNAs (Tuschl II 5:4-9).
- [22] According to Tuschl II, absence of a 2' OH group enhances the nuclease resistance of the overhang *in vitro* (Tuschl II 5:11-13).
- [23] For example, Tuschl II discloses that "[i]n preferred sugar-modified ribonucleotides the 2' OH-group is replaced by a group selected from H, OR, R, halo, SH, SR, NH₂, NHR, NR₂ or CN, wherein R is C₁-C₆ alkyl, alkenyl or alkynyl and halo is F, Cl, Br or I" (Tuschl II 5:31-6:2) as well as replacing uridine residues with 2' deoxy thymidine (*id.* 21:1-2; 40:19-29).
- [24] Referring to Figure 14, Tuschl II states that substitution of the 2-nt 3' overhangs by 2'-deoxy nucleotides (d) had no effect on RNAi activity and replacement of two additional ribonucleotides adjacent to the overhangs in the paired region left significant RNAi activity. However, complete substitution of one or both siRNA strands by 2'-

deoxy residues or by 2'-O-methyl residues abolished RNAi. (Tuschl II 46:5-14).

[25] Figure 4 of Tuschl II depicts the effect of substituting the 2'-hydroxyl groups of the siRNA ribose residues. The 2'-hydroxyl groups (OH) in the strands of siRNA duplexes were replaced by 2'-deoxy (d) or 2'-O-methyl (Me). 2-nt and 4-nt 2'-deoxy substitutions at the 3'-ends are indicated as 2-nt d and 4-nt d, respectively. Uridine residues were replaced by 2'-deoxy thymidine. [Tuschl II 20:28-21:2.] Figure 4 is reproduced below.



{Figure 14 of Tuschl II depicts the effect of substituting the 2'-OH groups of siRNA ribose residues.}

[26] Agrawal discloses antisense oligonucleotides that have increased resistance to nucleases, noting that even nuclease resistant 3' capped oligonucleotides can become degraded eventually as their 3' capped end is slowly digested by a combination of endonuclease and exonuclease activities (Agrawal 1:8-9; 3:4-26).

[27] In a preferred embodiment, Agrawal discloses oligonucleotides comprising a target hybridizing region and a self-complementary

region, wherein the self-complementary region is connected to the target hybridizing region by a non-nucleic acid linker, e.g., an (ethylene glycol)₁₋₆ linker (Agrawal 8:22-24; 15:31-36).

[28] Agrawal further discloses an embodiment wherein the oligonucleotide is hyperstabilized by incorporating one or more 2'-O-Me ribonucleotides into the self-complementary region and using DNA within the complementary portion of the target hybridizing region or vice versa because DNA:RNA interactions are more stable than DNA:DNA interactions (Agrawal 16:24-35).

[29] Matulic-Adamic discloses incorporating chemical modifications at the 5' and/or 3' ends of ribozymes, i.e., RNAs which can enzymatically cleave other RNA molecules in a nucleotide base specific manner, to protect the ends from exonuclease degradation (Matulic-Adamic 1:14-17; 2:44-54).

C. IKK- γ : its sequence and relationship to NF- κ B activation

[30] IKK- γ is also known as NEMO (NF- κ B Essential Modulator) (828 patent specification 8:31-32; Kenwrick 2:39-42; Krappmann abstract).

[31] NF- κ B plays a pivotal role in many cellular processes, including inflammation, the immune response, cell proliferation, and apoptosis (Krappmann 29779 ¶1).

[32] According to Krappmann, specific down regulation of IKK- γ protein levels by antisense oligonucleotides significantly reduced cytokine mediated activation of the IKK complex and subsequent NF- κ B activation (Krappmann abstract; 29780, col. 2, ¶2).

- [33] Kenwrick also discloses that the absence of IKK- γ protein results in a complete inhibition of NF- κ B activation (Kenwrick 2:42-46).
- [34] Yamaoka cloned a 48 kDa murine IKK- γ /NEMO protein and also found that it was essential for NF- κ B activation (Yamaoka abstract; 1233-1234 "Molecular Cloning of NEMO;" 1238, col. 2, ¶2).
- [35] Yamaoka deposited the NEMO cDNA sequence with GenBank under accession number AF069542 and provided the amino acid sequence of the protein in Figure 3 (Yamaoka 1234, 1240).
- [36] We find that it is well within ordinary skill in the art to access the publicly available gene sequence database GenBank (<http://www.ncbi.nlm.nih.gov/Genbank/index.html>) to obtain the NEMO cDNA sequence reported by Yamaoka under accession number AF069542.
- [37] Smahi discloses that most cases of familial incontinentia pigmenta (IP), a genodermatosis that is usually lethal prenatally in males and that causes abnormalities of the skin, hair, nails, teeth, eyes, central nervous system in affected females, are caused by mutations in the NEMO/IKK- γ gene (Smahi abstract).
- [38] Kenwrick discloses a method treating NF- κ B related medical conditions, such as IP, by administering therapeutically effective amounts of IKK- γ /NEMO nucleic acid of SEQ ID NO:1, a 23106 nt DNA (Kenwrick 4:24-28, 42-43; 49: <210> - <213>).
- [39] Kenwrick also discloses approximately sixty-seven sequences, generally about 20 nt in length, for use as primers and probes in

assays and kits for detecting mutations of SEQ ID NO:1 in an organism (Kenwick 5:33-7:29; SEQUENCE LISTING, cols. 73-90).

III. Discussion

As noted above, the pending rejections fall into two groups. While the primary references (i.e., Tuschl I, Ebashir (alone or in combination with Bass), or Fire) in each rejection of the first group are different, each rejection relies on common secondary (i.e., Tuschl II, Yamaoka, Krappmann, and Smahi) and tertiary (i.e., Agrawal and Matulic-Adamic) references, thereby raising common issues. Consequently, these rejections are addressed together.

A. The first group of rejections

1. Findings and conclusions of the Examiner

a. claim 1

As to claim 1, the Examiner found that Tuschl I teaches using 21-23 nt dsRNA molecules with 2'-deoxy modifications to mediate RNAi, if the sequence of the gene to be targeted is known, because siRNAs are effective at concentrations several orders of magnitude below concentrations used in conventional antisense or ribosome gene targeting experiments (Ans. 6).

The Examiner found that Tuschl I differs in failing to disclose siRNA molecules having both 2'-O-methyl and 2'-fluoro modifications (Ans. 6) and that down regulate the IKK- γ gene (Ans. 7).

The Examiner found that Elbashir teaches that 21 nt siRNAs with 2 nt 3' overhangs and 2'-thymidine modifications mediate RNAi at concentrations several orders of magnitude lower than concentrations used in conventional antisense or ribosome gene targeting experiments (Ans. 12).

The Examiner found that Bass teaches that once the sequence of gene is known, RNAi may be used to determine its function, that RNAi is a routine technology, and that siRNA mediated RNAi triggers degradation of mRNA at concentrations several orders of magnitude lower than concentrations used in conventional antisense or ribosome gene targeting experiments (Ans. 13). The Examiner found that Elbashir differs in failing to disclose siRNA molecules having both 2'-O-methyl and 2'-fluoro modifications (Ans. 12) and that neither Elbashir nor Bass disclose siRNAs that down regulate the IKK- γ gene (Ans. 13).

The Examiner found that Fire discloses dsRNA mediated inhibition of gene expression, wherein the dsRNA comprised (i) at least 25 base pairs, (ii) complementary sense and antisense strands, the antisense strand being at least 90% complementary to the nucleotide sequence of a target gene, and (iii) optionally, one or more modifications to either the phosphate-sugar backbone or nucleoside (Ans. 16). The Examiner found that Fire discloses that dsRNA mediated RNAi is at least 100-fold more effective than an equivalent concentration of antisense RNA in reducing gene expression (Ans. 17). The Examiner found that Fire differs in failing to disclose siRNA molecules having both 2'-O-methyl and 2'-fluoro modifications and that down regulate the IKK- γ gene (Ans. 17).

The Examiner found that Tuschl II teaches 19-25 nt dsRNAs with 3' end overhangs which act as guide RNAs for sequence specific mRNA degradation and show high stability *in vivo* or *in vitro* (Ans. 6, 12, 1). The Examiner also found that Tuschl II teaches substituting 2' OR (wherein R is

C₁₋₆ alkyl) and/or fluoro groups for the 2' OH groups of the RNA sugars (Ans. 6-7, 13, 17).

The Examiner found that Yamaoka discloses the cDNA sequence encoding a 48 kDa IKK- γ protein (Ans. 7, 13, 17).

The Examiner found that Krappmann discloses that specific down regulation of IKK- γ protein levels by antisense oligonucleotide significantly reduced cytokine mediated activation of IKK complex and subsequent NF- κ B activation (Ans. 7, 13, 18).

The Examiner found that Smahi identifies the IKK- γ gene as target for experimental gene silencing because mutations in this gene are associated with the genetic disease IP (Ans. 7, 14, 18).

The Examiner found that the level of skill in the art is high (Ans. 8, 14, 18).

The Examiner concluded that it would have been obvious to combine the teachings of Tuschl I or Elbashir or Fire with the teachings of Tuschl II to produce chemically modified, stable ds siRNA (Ans. 7, 13, 17). The Examiner further concluded that it would have been obvious to combine the teachings of Tuschl I or Elabshir or Fire with the teachings of Tuschl II and with the teachings of Smahi, Krappmann, and Yamaoka to produce siRNA molecules that down regulate the IKK- γ gene because Krappmann discloses antisense mediated down regulation of the IKK- γ gene, Smahi teaches that the IKK- γ gene is a desirable target, and Tuschl I, Elbashir, and Fire each teach that siRNAs are more powerful than conventional antisense or ribozyme mediated gene targeting experiments (Ans. 7-8, 14, 18). The Examiner concluded that one of ordinary skill in the art would have had a

reasonable expectation of success of producing chemically modified siRNA molecules that down regulate the IKK- γ given the teachings of the applied references and the high level of skill in the art.

b. claim 4

As to claim 4, the Examiner found that none of Tuschl I, Elbashir, Bass, Fire, Tuschl II, Smahi, Krappmann or Yamaoka discloses connecting the sense and antisense strands of the siRNA by a linker (Ans. 8, 14, 18).

The Examiner found that Agrawal discloses antisense oligonucleotides with increased resistance to degradation by nucleases, including both exo- and endo-nucleases; and, which formed stable hybrids with target sequences and activated RNase H (i.e., mediated RNAi) (Ans. 8, 14, 19). The Examiner found that the antisense oligonucleotide of Agrawal contained (i) a self-complementary region which self-paired, resulting in formation of a hairpin loop containing a polynucleotide linker; and, (ii) a target hybridization region which may be connected to the self-complementary region via a non-nucleic acid linker (Ans. 8, 15, 19).

The Examiner concluded that it would have been obvious to combine the teachings of Agrawal with the teachings of the references applied against claim 1 because Agrawal suggests forming stable, nuclease-resistant duplexes using linkers capable of mediating RNAi (Ans. 8, 15, 19).

c. claim 7

As to claim 7, the Examiner found that none of Tuschl I, Elbashir, Bass, Fire, Tuschl II, Smahi, Krappmann or Yamaoka discloses fragments [sic, overhangs?] comprising terminal caps (Ans. 9, 15, 19).

The Examiner found that Matulic-Adamic discloses chemically capping the 5' and/or 3' ends of ribozymes, i.e., nucleic acids that are particularly use for enzymatic cleavage of RNA, to protect the ribozyme from exonuclease degradation (Ans. 9, 15, 19).

The Examiner concluded that it would have been obvious to combine the teachings of Matulic-Adamic with the teachings of the references applied against claim 1, i.e., to end cap the siRNA, because Matulic-Adamic teaches that end capping protects against exonuclease degradation (Ans. 9, 15, 19-20).

2. Appellant's arguments

Initially, we note that arguments based on evidence which has not been cited as relied upon in the Evidence Appendix of the principal brief or provided therewith have not been considered. 37 C.F.R. § 41.37(c)(2)(ix).

a. claim 1

In essence, Appellant argues that there was little, if any, reason for one of ordinary skill in the art to modify siRNAs with both 2'-O-methyl and 2'-deoxy-2'-fluoro modifications because one could not have predicted which modifications might be efficacious and because Tuschl II was said to teach away for the claimed modification (App. Br. 12-13).

Specifically Appellant argues that Tuschl II expressly warns against using more than two 2'-deoxy modified nucleotides at the strands' 3'-ends or using any 2'-O-methyl modifications, i.e.:

2'-deoxy substitutions of the 2-nt 3' overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNase resistance of siRNA duplexes. More extensive 2'-deoxy or 2'-O-methyl

modifications, however, reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNAP assembly. [Tuschl II 49:28-50:2.]

(App. Br. 13). Appellant further argues that since Tuschl II fails to state expressly the effect of 2'-O-methyl substitution on page 46, Tuschl II can only be read teaching the entire avoidance of 2'-O-methyl modifications (App. Br. 13). Thus, Appellant concludes:

[b]ecause 2'-deoxy and 2'-O-methyl modifications were regarded as beneficial to other nucleic acid inhibitors known in the art at the time, and these modifications are found by Tuschl to be not tolerated at all (in the case of 2'-O-methyl modification), or under very limited circumstances (in the case of 2'-deoxy modification), the art of chemically modifying siRNA molecules was highly unpredictable, and the ... ribozyme and/or antisense art predating the present invention does nothing to alleviate this unpredictability. [App. Br. 14.]

Appellant further argues that since Smahi shows that mutation of the IKK- γ gene result in death or disease, one skilled in the art would not have been motivated to down regulate the IKK- γ gene unless he was interested in causing death or disease (App. Br. 14-15). Appellant points out that Elbashir fails to disclose an siRNA that down regulates IKK- γ gene (App. Br. 19).

Appellant also argues that Yamaoka does not disclose an IKK- γ cDNA sequence (App. Br. 15).

Appellant argues that Bass teaches that RNAi can occur by different pathways, one mediated by long dsRNA (at least 30 nt in length) molecules

and the other by short dsRNA (siRNA) molecules; and, that Bass' reference to RNAi as a routine laboratory procedure refers to the long dsRNA pathway (App. Br. 19, 21). Thus, Appellant reasons, one of ordinary skill in the art would have understood Fire to have mistakenly stated that dsRNA molecules of 25 nt in length were operative because dsRNA molecules smaller than 30 nts were inoperative (App. Br. 21).

b. claim 4

Appellant argues that antisense molecules are substantially single stranded prior to interacting with their target and, thus, more susceptible to nuclease attack than is a double stranded nucleic acid molecule (App. Br. 16). Moreover, when Tuschl II limited applicability of 2'-deoxy modifications and avoidance of 2'-O-methyl modifications are considered, Agrawal does not inform or lend predictability to the art of chemically modified siRNA molecules (App. Br. 16). [See also App. Br. 20, 22.]

c. claim 7

In a similar vein, Appellant argues that ribozymes are substantially single stranded prior to interacting with their target and, thus, more susceptible to nuclease attack than is a double stranded nucleic acid molecule (App. Br. 17). Moreover, when Tuschl II limited applicability of 2'-deoxy modifications and avoidance of 2'-O-methyl modifications are considered, Matulic-Adamic does not inform or lend predictability to the art of chemically modified siRNA molecules (App. Br. 17-18). [See also App. Br. 20, 22.]

3. Legal principles

“Section 103 forbids issuance of a patent when ‘the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.’” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406, 127 S. Ct. 1727 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including (1) the scope and content of the prior art, (2) any differences between the claimed subject matter and the prior art, (3) the level of skill in the art, and (4) where in evidence, so-called secondary considerations. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). In *KSR*, the Supreme Court reaffirmed principles based on its precedent that “[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *KSR*, 550 U.S. at 416. The Court emphasized that “rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness” *id.* at 418 (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). However, “the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *Id.* Thus, “[i]n considering motivation in an obviousness analysis, we ask ‘whether a person of ordinary skill in the art, possessed with the understandings and knowledge reflected in the prior art,

and motivated by the general problem facing the inventor, would have been led to make the combination recited in the claims.'" *Optivus Tech., Inc. v. Ion Beam Applications S.A.*, 469 F.3d 978, 990 (Fed. Cir. 2006) (citing *In re Kahn*, 441 F.3d at 988). "Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references." *In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986).

4. Analysis

Here, Tuschl I, Elbashir, and Fire each teach dsRNAs about 18 to about 28 nucleotides in length (FF 7, 10, 13, 15, 16) that mediate RNAi (FF 3, 4, 7-8, 9-10, 12, 15) at concentrations several orders of magnitude below the concentrations needed in conventional antisense or ribozyme gene targeting experiments and, thus, suggest the usefulness of these siRNAs in gene targeting experiments (FF 5, 6). Gene targeting may be used to inhibit expression of a gene associated which encodes a protein associated with or causative of disease or other undesirable conditions or to study the function of gene (FF 2, 8). Tuschl II discloses siRNA duplexes 19-25 nucleotides in length that mediate RNAi (FF 19) and a proposed molecular explanation of how siRNA mediated RNAi works (FF 19).

Tuschl I and Tuschl II teach and/or suggest that the most effective siRNA molecules comprise two 21 nt strands which are base paired such that 1-3, especially 2 nt 3' overhangs are present on both ends of the siRNA duplex (FF 13, 18). Thus, each strand of the siRNA is single-stranded in its 3' overhang. According to both Tuschl I and Tuschl II, the absence of a 2'-OH group enhances the nuclease resistance of the 3' overhang (FF 14, 22).

Moreover, Fire, Tuschl I, Elbashir, and Tuschl II each teach the siRNA may include modifications to phosphate-sugar backbone and/or nucleoside (FF 7, 13, 16, 21).

Modifications of nucleic acids to stabilize them against degradation by nucleases was known in the art. Tuschl II preferably substitutes the 2'-OH groups of 3' overhang (i.e., single stranded) portion of siRNAs with OR groups to form C₁₋₆ alkyl ester groups, e.g., methyl esters, and halide groups, e.g., fluoro, as well as replacing uridine residues with 2'-deoxy thymidines, to enhance the nuclease resistance of the overhang portion (FF 23).

Similarly, Matulic-Adamic chemically modifies the 5' and/or 3' ends of ribozymes to protect them from exonuclease degradation (FF 29). Agrawal notes that even nuclease resistant 3' capped oligonucleotides can become degraded eventually as their 3' capped end is slowly digested by a combination of endonuclease and exonuclease activity (FF 26) and discloses antisense oligonucleotides wherein regions of the antisense are connected via linkers (FF 27).

Therefore, we agree with the Examiner that it would have been obvious to modify an siRNA, particularly at nucleotides in a 1-3 nt of a 3' overhang at the end of one or both strands, to increase the resistance of siRNA to nuclease degradation using modifications known and used for increasing the stability of RNA to nuclease degradation. We also agree with the Examiner that it would have been obvious to select an IKK- γ as a gene for targeted experimentation because of its known relationship with NF- κ B activation as disclosed by Krappmann (FF 32) and/or its causal relationship

to IP as disclosed by Smahi (37) given Yamaoka's disclosed cDNA and amino acid sequences for an IKK- γ gene (FF 34-36).

Appellant's arguments do not persuade us to the contrary.

Nucleic acid molecules are known to be degraded or hydrolyzed by nucleases *in vivo* and in culture systems and, thus, it is routine in the art to modify nucleic acids to resist nuclease hydrolysis (see e.g., FF 16, 21, 26, 29). Exonucleases by definition hydrolyze nucleic acid molecules from their ends, while endonucleases attack nucleic molecules between their ends. Modifications which interfere with the interaction between a nucleotide substrate and a nuclease enzyme's active site would reasonably be expected to increase a nucleic acid's resistance to nuclease degradation. Thus, it is not unexpected, and in fact is entirely predictable, that a double stranded nucleic acid would be less susceptible to nuclease degradation than a single stranded nucleic acid since one strand would reasonably be expected to block a nuclease's, particularly an endonuclease's, access to the other strand to some degree. Indeed, Appellant even points out that single stranded nucleic acids are more susceptible to nuclease degradation than double stranded nucleic acids (see e.g., App. Br. 16-17). Similarly, capping one or both ends of a nucleic acid molecule, as disclosed by Matulic-Adamic, or forming a double-stranded portion within an antisense molecule, as disclosed by Agrawal, would also reasonably be expected to sterically interfere with the active site of a nuclease. By the same token, the most effective siRNA molecules are disclosed as having 3' overhangs (see e.g., FF 13, 18) and, therefore, would reasonably be expected to be more susceptible to nuclease degradation by virtue of being single stranded structures. Moreover, Tuschl

I and Tuschl II identify a specific site of nuclease attack, i.e., the 2'-OH group of the nucleotide (FF 14, 22). Therefore, it would have been obvious to modify the 2'-OH group of the 3' overhang of siRNAs to increase the nuclease resistance of the siRNA. The combination of chemical modifications known to increase the nuclease resistance of nucleic acid molecules to siRNA molecules, particularly to the 2'-OH group of a single stranded 3' overhang, is likely to be obvious when it does no more than yield a predictable result.

Furthermore, claim 1 only requires the recited siRNA to have a single 2'-O-methyl modification and a single 2'-fluoro modification. For example, if the siRNA had a 3 nt 3' overhang, the end nucleotide might be modified with a 2'-O-methyl group and the middle nucleotide of the overhang might be modified with a 2'-fluoro group. However, overmodification of the 2'-OH groups is expressly warned against by Tuschl II, e.g., complete substitution of the 2'-OH groups of one or both siRNA strands abolishes RNAi (FF 24). Moreover, Tuschl II teaches that the 3' overhang does not contribute to specificity of the target recognition (FF 19), a teaching which have reasonably suggested that chemical modifications to the 3' overhang would be less likely to interfere with the efficacy of the siRNA. Indeed, this appears to be consistent with the data presented in the bar graph of Tuschl II Figure 4 (FF 25). Thus, even assuming *arguendo* that Tuschl II warned against modifying more than two 2'-OH groups at the 3' ends of the siRNA, this argument is not convincing because modifying just two 2'-OH groups at the 3' overhangs (ends) of the siRNA is within the scope of the claimed invention.

Appellant's argument that Tuschl II teaches avoiding any 2'-O-methyl modifications (App. Br. 13) is likewise unpersuasive and misstates Tuschl II. A fair reading of Tuschl II at column 49, line 28, through column 50, line 2, as pointed out by the Examiner (see e.g., Ans. 22), is that more extensive 2'-deoxy or 2'-O-methyl modifications beyond the two nucleotide 3' overhang reduces the ability of siRNAs to mediate RNAi. Moreover, stating that *complete* substitution of one or both siRNA stands by 2'-O-methyl groups abolished RNAi (FF 24), is not synonymous with stating that *any* 2'-O-methyl group modification should be avoided. Therefore, this argument is not persuasive.

Appellant's argument that Smahi fails to provide a motivation for targeting an IKK- γ gene for down regulation by RNAi because down regulated an already defective gene could cause death or disease is unpersuasive for a number of reasons. The Examiner is relying on the combination of Krappmann and Smahi as a reason to study a down regulated IKK- γ gene. As noted by the Examiner (Ans. 25), Krappmann discloses the importance of down regulating an IKK- γ gene, i.e., down regulating IKK- γ reduces subsequent NK- κ B activation, which plays a pivotal response in cellular processes, e.g., inflammation (FF 31-32). Thus, the Examiner essentially concluded that it would have been obvious to down regulate or knock down an IKK- γ gene to study the effect on cellular processes, e.g., inflammation. Smahi discloses that most cases of IP are caused by mutations in the IKK- γ gene (FF 37). The Examiner again found that the IKK- γ gene is a desirable gene for experimental gene silencing (Ans. 7, 14, 18). Thus, the Examiner evidently concluded that it would have been

obvious to experimentally silence an IKK- γ gene to provide a knock-down experimental IP study system. Therefore, Krappmann and/or Smahi suggest studying the IKK- γ gene by experimental silencing. Moreover, the claimed invention is not directed to treating any specific disease or condition by administering a therapeutically effective amount of an IKK- γ gene down regulating siRNA. Therefore, this argument is not persuasive.

Next, Appellant is correct that Yamaoka did not expressly recite the cDNA sequence he obtained. However, Yamaoka expressly stated that the cDNA sequence was deposited with GenBank under accession number AF069542 (FF 35), which is analogous to a deposit of biological material made to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. It would have been well within ordinary skill in the art, which as the Examiner noted is high, to obtain the deposited cDNA sequence from the publicly available GenBank database (FF36). This is entirely routine and predictable (FF36). Alternatively, Yamaoka expressly disclosed the amino acid sequence of the protein encoded by the cDNA (FF 35), thereby providing a generic description of the DNA sequences encoding the IKK- γ protein. *See e.g., In re Wallach*, 378 F.3d 1330, 1333-34 (Fed. Cir. 2004) (an amino acid sequence supports the entire genus of DNA sequences that can encode the amino acid sequence because the state of the art has developed such that it is routine matter to convert one to the other). Therefore, Appellant's argument that Yamaoka did not disclose an IKK- γ cDNA sequence is not well taken.

Finally, Appellant's argument that one of ordinary skill in the art would interpret Fire as inoperative for dsRNAs of 25 nucleotides in length is

not persuasive. A patent is presumed valid. 35 U.S.C. § 282. In addition, claim 10 of Fire expressly recites a method of RNAi wherein the dsRNA is at least 25 bases in length (FF 7). "The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity." 35 U.S.C. § 282. Appellant's conclusory statement that one of ordinary skill in the art would have understood Fire to be mistaken in its specification and claims is insufficient to meet this burden. *In re Schulze*, 346 F.2d 600, 602 (CCPA 1965) (argument in the brief does not take the place of evidence of record).

Based on the foregoing, we sustain the rejections of claims 1-3, 14, and 16 under § 103 over the combined teachings of Tuschl I, Tuschl II, Yamaoka, Smahi, and Krappmann; claims 4-6 under § 103 over the combined teachings of Tuschl I, Tuschl II, Yamaoka, Smahi, Krappmann, and Agrawal; claims 7 and 8 under § 103 over the combined teachings of Tuschl I, Tuschl II, Yamaoka, Smahi, Krappmann, and Matulic-Adamic;

claims 1-3 and 14-16 under § 103 over the combined teachings of Elbashir, Tuschl II, Bass, Yamaoka, Krappmann, and Smahi; claims 4-6 under § 103 over the combined teachings of Elbashir, Tuschl II, Bass, Yamaoka, Krappmann, Smahi, and Agrawal; claims 7-8 under § 103 over the combined teachings of Elbashir, Tuschl II, Bass, Yamaoka, Krappmann, Smahi, and Matulic-Adamic;

claims 1-3, 9, and 14-16 under § 103 over the combined teachings of Fire, Tuschl II, Yamaoka, Krappmann, and Smahi; (I) claims 4-6 under § 103 over the combined teachings of Fire, Tuschl II, Yamaoka, Krappmann,

Smahi, and Agrawal; and, claims 7-8 under § 103 over the combined teachings of Fire, Tuschl II, Yamaoka, Krappmann, Smahi, and Matulic-Adamic.

B. The second group of rejections

The second group of rejections only contains a single rejection, i.e., claims 1-3 are rejected under § 103 over the combined teachings of Kenwick, Tuschl I, and Tuschl II.

1. Findings and conclusions of the Examiner

The Examiner found that Kenwick teaches methods of treating NK- κ B related medical conditions by administering therapeutically effective amounts of SEQ ID NO:1 (Ans. 10, 32). Kenwick SEQ ID NO:1 is a 23106 nt IKK- γ DNA sequence (FF 38). The Examiner also found that Kenwick discloses "a large number of short nucleic acids," five of which are 100% complementary to an IKK- γ mRNA (SEQ ID NOs:49, 50, 54, 56, and 61) (Ans. 10). The Examiner found that Kenwick differs in failing to disclose siRNA molecules comprising 2'-O-methyl and 2'-fluoro group modifications, wherein the siRNA molecules also down regulate expression of the IKK- γ gene (Ans. 10).

The Examiner concluded that it would have been obvious to produce double stranded siRNA molecules that down regulate IKK- γ gene expression since Kenwick teaches IKK- γ gene sequences and Tusch I and Tuschl II teach methods of producing chemically modified double stranded siRNA molecules (Ans. 10-11, 32-33).

2. Appellant's arguments

Appellant argues that Kenwick teaches DNA fragments which are used as primers to amplify and detect IKK- γ nucleic acids and that Kenwick does not teach down regulation of IKK- γ gene expression for any reason. In essence, Appellant argues the rejection of claims 1-3 over Kenwick, Tuschl I, and Tuschl II is a classic hindsight reconstruction of the claimed invention.

3. Legal principles

"One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

4. Analysis

Here, we agree with Appellant. Kenwick discloses a method of treating NK- κ B related medical conditions by administering therapeutically effective amounts of the IKK- γ gene, i.e., SEQ ID NO:1 (FF 38). Implicitly, Kenwick is seeking to correct an abnormal IKK- γ gene. This interpretation is consistent with Kenwick's disclosure of well over sixty short DNA sequences as primers and probes in assays and kits for detecting mutations in SEQ ID NO:1, i.e., the IKK- γ gene (FF 39). The Examiner has failed to explain why Kenwick would have suggested down-regulating a gene that he is trying to repair, i.e., replace with SEQ ID NO:1. Rather, it appears that the Examiner has fallen into the trap of hindsight reconstruction.

Based on the foregoing, we reverse the rejection of claims 1-3 under § 103 over the combined teachings of Kenwick, Tuschl I, and Tuschl II.

D. Conclusion

Appellant has failed to show the Examiner reversibly erred in (i) finding that Yamaoka disclosed the cDNA sequence of an IKK- γ gene, (ii) concluding that an ordinarily skilled artisan would have had both a motivation to and a reasonable expectation of success of providing an siRNA molecule with at least one 2'-O-methyl group and at least one 2'-fluoro group, (iii) failing to provide a reason for down regulating an IKK- γ gene, (iv) concluding that it would have been obvious to join a sense and an anti-sense RNA strand into a single ds siRNA via a linker molecule based on the teachings of Agrawal, or (v) concluding that it would have been obvious to cap either or both ends of the antisense strand based on the teachings of Matulic-Adamic. However, Appellant has shown that the Examiner reversibly erred in (vi) concluding that Kenwrick provided a teaching or suggestion of down regulating IKK- γ gene expression.

IV. Order

Upon consideration of the record, and for the reasons given, it is

ORDERED that the decision of the Examiner to reject claims 1-3, 14, and 16 under 35 U.S.C. § 103(a) as unpatentable over Tuschl I and Tuschl II in view of Yamaoka, Smahi, and Krappmann is AFFIRMED;

FURTHER ORDERED that the decision of the Examiner to reject claims 4-6 under 35 U.S.C. § 103(a) as unpatentable over Tuschl I, Tuschl II, Yamaoka, Smahi, and Krappmann taken further in view of Agrawal is AFFIRMED;

FURTHER ORDERED that the decision of the Examiner to reject claims 7 and 8 under 35 U.S.C. § 103(a) as unpatentable over Tuschl I,

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Tuschl II, Yamaoka, Smahi, and Krappmann taken further in view of Matulic-Adamic is AFFIRMED;

FURTHER ORDERED that the decision of the Examiner to reject claims 1-3 under 35 U.S.C. § 103(a) as unpatentable over Kenwick in view of Tuschl I and Tuschl II is REVERSED;

FURTHER ORDERED that the decision of the Examiner to reject claims 1-3 and 14-16 under 35 U.S.C. § 103(a) as unpatentable over Elbashir, Tuschl II, and Bass in view of Yamaoka, Krappmann, and Smahi is AFFIRMED;

FURTHER ORDERED that the decision of the Examiner to reject claims 4-6 under 35 U.S.C. § 103(a) as unpatentable over Elbashir, Tuschl II, Bass, Yamaoka, Krappmann, and Smahi further in view of Agrawal is AFFIRMED;

FURTHER ORDERED that the decision of the Examiner to reject claims 7-8 under 35 U.S.C. § 103(a) as unpatentable over Elbashir, Tuschl II, Bass, Yamaoka, Krappmann, and Smahi further in view of Matulic-Adamic is AFFIRMED;

FURTHER ORDERED that the decision of the Examiner to reject claims 1-3, 9, and 14-16 under 35 U.S.C. § 103(a) as unpatentable over Fire and Tuschl II in view of Yamaoka, Krappmann, and Smahi is AFFIRMED;

FURTHER ORDERED that the decision of the Examiner to reject claims 4-6 under 35 U.S.C. § 103(a) as unpatentable over Fire, Tuschl II, Yamaoka, Krappmann, and Smahi further in view of Agrawal is AFFIRMED;

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FURTHER ORDERED that the decision of the Examiner to reject claims 7-8 under 35 U.S.C. § 103(a) as unpatentable over Fire, Tuschl II, Yamaoka, Krappmann, and Smahi further in view of Matulic-Adamic is AFFIRMED; and,

FURTHER ORDERED that requests for extending time for taking any subsequent action in connection with this appeal are governed by 37 C.F.R. § 1.550(c).

AFFIRMED

Ack

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Lehninger **PRINCIPLES OF BIOCHEMISTRY**

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INFORMATION PATHWAYS

Genes and Chromosomes	923
DNA Metabolism	948
RNA Metabolism	995
Protein Metabolism	1034
Regulation of Gene Expression	1081

The third and final part of this book explores the biochemical mechanisms underlying the apparently contradictory requirements for both genetic continuity and the evolution of living organisms. What is the molecular nature of genetic material? How is genetic information transmitted from one generation to the next with high fidelity? How do the rare changes in genetic material that are the raw material of evolution arise? How is genetic information ultimately expressed in the amino acid sequences of the astonishing variety of protein molecules in a living cell?

The fundamental unit of information in living systems is the **gene**. A gene can be defined biochemically as a segment of DNA (or, in a few cases, RNA) that encodes the information required to produce a functional biological product. The final product is usually a protein, so much of the material in Part III concerns genes that encode proteins. A functional gene product might also be one of several classes of RNA molecules. The storage, maintenance, and metabolism of these informational units form the focal points of our discussion in Part III.

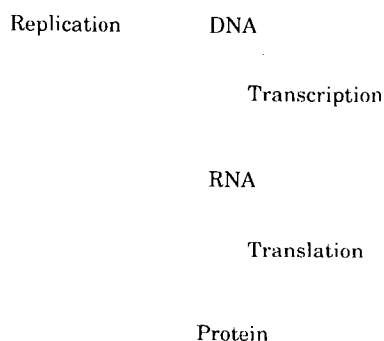
Modern biochemical research on gene structure and function has brought to biology a revolution comparable to that stimulated by the publication of Darwin's theory on the origin of species nearly 150 years ago. An understanding of how information is stored and used in

cells has brought penetrating new insights to some of the most fundamental questions about cellular structure and function. A comprehensive conceptual framework for biochemistry is now unfolding.

Today's understanding of information pathways has arisen from the convergence of genetics, physics, and chemistry in modern biochemistry. This was epitomized by the discovery of the double-helical structure of DNA, postulated by James Watson and Francis Crick in 1953 (see Fig. 8-15). Genetic theory contributed the concept of coding by genes. Physics permitted the determination of molecular structure by x-ray diffraction analysis. Chemistry revealed the composition of DNA. The profound impact of the Watson-Crick hypothesis arose from its ability to account for a wide range of observations derived from studies in these diverse disciplines.

This revolution in our understanding of the structure of DNA inevitably stimulated questions about its function. The double-helical structure itself clearly suggested how DNA might be copied so that the information it contains can be transmitted from one generation to the next. Clarification of how the information in DNA is converted into functional proteins came with the discovery of both messenger RNA and transfer RNA and with the deciphering of the genetic code.

These and other major advances gave rise to the central dogma of molecular biology, comprising the three major processes in the cellular utilization of genetic information. The first is **replication**, the copying of parental DNA to form daughter DNA molecules with identical nucleotide sequences. The second is **transcription**, the process by which parts of the genetic message encoded in DNA are copied precisely into RNA. The third is **translation**, whereby the genetic message encoded in messenger RNA is translated on the ribosomes into a polypeptide with a particular sequence of amino acids.



The central dogma of molecular biology, showing the general pathways of information flow via replication, transcription, and translation. The term "dogma" is a misnomer. Introduced by Francis Crick at a time when little evidence supported these ideas, the dogma has become a well-established principle.

Part III explores these and related processes. In Chapter 24 we examine the structure, topology, and packaging of chromosomes and genes. The processes underlying the central dogma are elaborated in Chapters 25 through 27. Finally, we turn to regulation, examining how the expression of genetic information is controlled (Chapter 28).

A major theme running through these chapters is the added complexity inherent in the biosynthesis of macromolecules that contain information. Assembling nucleic acids and proteins with particular sequences of nucleotides and amino acids represents nothing less than preserving the faithful expression of the template

upon which life itself is based. We might expect the formation of phosphodiester bonds in DNA or peptide bonds in proteins to be a trivial feat for cells, given the arsenal of enzymatic and chemical tools described in Part II. However, the framework of patterns and rules established in our examination of metabolic pathways thus far must be enlarged considerably to take into account molecular information. Bonds must be formed between *particular* subunits in informational biopolymers, avoiding either the occurrence or the persistence of sequence errors. This has an enormous impact on thermodynamics, chemistry, and enzymology of biosynthetic processes. Formation of a peptide bond requires an energy input of only about 21 kJ/mol of bond and can be catalyzed by relatively simple enzymes. To synthesize a bond between two specific amino acids at a particular point in a polypeptide, the cell invests about 125 kJ/mol while making use of more than 20 enzymes, RNA molecules, and specialized proteins. The chemistry involved in peptide bond formation does not change because of this requirement, but additional processes are layered over the basic reaction to ensure that the peptide bond is formed between particular amino acids. Information is expensive.

The dynamic interaction between nucleic acids and proteins is another central theme of Part III. With the important exception of a few catalytic RNA molecules (discussed in Chapters 26 and 27), the processes that make up the pathways of cellular information flow are catalyzed and regulated by proteins. An understanding of these enzymes and other proteins can have practical as well as intellectual rewards, because they form the basis of recombinant DNA technology (introduced in Chapter 9).

APPENDIX D

AMENDMENTS IN THE CLAIMS

None